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MRI DISPLAYS THE PROSTATIC CANCER ANATOMY AND IMPROVES THE BUNDLES MANAGEMENT BEFORE ROBOT ASSISTED RADICAL PROSTATECTOMY

Running title: mpMRI-guided NS surgery in robotic prostatectomy

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ABSTRACT

Objectives: To evaluate the impact of multiparametric magnetic resonance imaging (mpMRI) to guide the nerve sparing (NS) surgical plan in prostate cancer (PCa) patients referred to robot assisted radical prostatectomy (RARP)

Methods: 137 consecutive PCa patients were submitted to RARP between September 2016 and February 2017 at two high-volume European centers. Before RARP, each patient was referred to 1.5-T or 3.0 T mpMRI. NS was recorded as Grade 1, Grade 2, Grade 3 and Grade 4 according to Tewari et al.[11] classification. A preliminary surgical plan to determinate the extent of NS approach was recorded basing on clinical data. The final surgical plan was re-assessed after mp-MRI revision. The appropriateness of surgical plan change was considered basing on the presence of ECE or positive surgical margins (PSMs) at level of NVBs area at final pathology. Furthermore, we analyzed a control group during the same period of 166 PCa patients referred to RARP in both institutions without preoperative mpMRI to assess the impact of the use of mpMRI on the surgical margins.

Results: Considering 137 patients with preoperative mpMRI, the mpMRI revision induced the main surgeon to change the NS surgical plan in 46.7% of cases on patient-based and 56.2% and on side-based analysis. The surgical plan change results equally assigned between the direction of more radical and less radical approach both on patient-based (54.7% vs. 54.3%) and on side-based levels (50% vs. 50%), resulting an overall appropriateness of 75%. Moreover, patients staged with mpMRI revealed significant lower overall PSMs as compared with control group with no mpMRI (12.4% vs. 24.1%; $p \leq 0.01$)

Conclusions: MpMRI induces robotic surgeons to change the surgical plan in almost half of individuals thus tailoring the NS approach, without compromising the oncologic outcomes. Compared to patients treated without mpMRI, the use of preoperative mpMRI can significantly reduce the overall PSMs.

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INTRODUCTION

With the advent of robotic surgery, surgical treatment of prostate cancer (Pca) has become more and more "conservative"[1-3] and many patients expect to recovery back to baseline erectile function status. In this contest, a correct nerve sparing (NS) approach should obtain the optimal compromise between a radical resection of the neurovascular bundle (NVB) with risk of impotence and extreme preservation of NVB with risk of positive surgical margins (PSMs). The ability to define the precise tumor's anatomy and the prediction of the probability of extracapsular extension (ECE) represent the keystone of proper surgical management, especially with robotic technology since lack of tactile sensation may compromise the surgeon's perception of potential capsular involvement[4].

The clinical parameters including preoperative prostate specific antigen (PSA) levels, clinical stage based on digital rectal examination (DRE) and transrectal ultrasound (TRUS) as well as biopsy Gleason score are independent predictors of pathological stage at radical prostatectomy (RP) specimens. Some clinical nomograms has been developed in order to assess the risk of ECE[5], showing a performance accuracy up to 68% even in external validation cohorts[6]. Clinical features have been represented the main tools aimed to guide surgeons during RP for years. However, these preoperative clinical parameters are suboptimal to predict the correct extension of the disease and to choose the proper surgical plan, especially when NS approach is attempted. To overcome this limitation, multiparametric Magnetic Resonance Imaging (mpMRI) including functional phases proved to be an optimal tool to predict the real tumour anatomy thus improving the local staging in PCa[7] with an accuracy in the prediction of ECE up to 80%,[8],[9,10].

In attempt to balance the competing goals of oncologic cure and sexual recovery, Tewari et al.[11] proposed a risk-stratified approach for NVB preservation during robot assisted radical prostatectomy (RARP), based on several pre-operative parameters including mpMRI findings, suggesting to improve potency outcomes without compromise PSMs rates. Many recent studies suggest that mpMRI can change the clinical approach regarding preservation or resection of NVBs during RARP in approximately one out three individuals[9,12,13]. Under this light, we aimed to report the clinical impact of preoperative

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mpMRI concerning NS surgery in a cohort of consecutive PCa patients treated at two high-volume robotic centres, evaluating the appropriateness of surgical plan changing. Furthermore, we compared the rate of PSM in patients treated with preoperative mpMRI compared to a cohort not submitted to mpMRI.

MATERIALS AND METHODS

Patients population

Overall, we prospectively identified 137 consecutive patients with biopsy-proven PCa and preoperative normal erectile function (International Index of Erectile Function questionnaire>21[14]), who underwent RARP between September 2016 and February 2017. Before RARP, each patient was referred to 1.5-T mpMRI using endorectal coil or 3.0 T mpMRI to improve local staging assessment and to guide surgeon during NS surgery. Patients with prior hormonal or radiation therapy were excluded. Each patient included had complete preoperative, intraoperative and pathologic parameters. A control group of 166 PCa patients referred to RARP in both institution in the same period without preoperative mpMRI was evaluated. The study was in line with the local institutional ethical committees.

MRI imaging

All the MRI examinations were performed with a 1.5T whole body scanner (Signa HDxt; GE Healthcare, Milwaukee, WI, USA) and a standard 8-channel pelvic phased-array surface coil combined with a disposable endorectal coil (MedRad, Indianola, Pa, or with a 3.0 T whole body scanner (Signa HD; GE Healthcare; Buckinghamshire, UK) without endorectal coil.

Morphological study of the prostate gland were obtained with the Fast Relaxation Fast Spin Echo (FRFSE) and Turbo Spin Echo (TSE) T2-weighted sequences in the sagittal, axial and coronal planes, including seminal vesicles and the entire prostate gland, with a slice thickness of 3 mm. For the functional study, DWI and DCE-MRI acquisition were performed.

All the mpMRI images were assessed by one single expert uro-radiologist reader per each center, with at least 10-years of specific experience on prostate MRI who was blinded to all

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patient information. All lesions were scored using the PI-RADS-v2 according to the ESUR guidelines[15]. The criteria for ECE included irregular capsular bulging, asymmetric NVB, obliterated rectoprostatic angle, overt extracapsular tumor and periprostatic infiltration. The criterion for SVI was a hypointense lesion in one or both seminal vesicles[13,16]. The probability of ECE was assessed using a Likert-like scale between 1 and 5 (1: definitely not present; 2: probably not present; 3: equivocal; 4: probably present; 5: definitely present). The assigned scores ≥ 4 were considered positive for ECE[17].

Pathologic examination

Whole-mounted histological sections of prostate glands and seminal vesicles were used as the reference standard. One single experienced uro-pathologist per each center evaluated all surgical specimens assessing the presence or absence of tumor, size, tumor location and side, Gleason score, surgical margin status, Gleason score at margins' level and the presence of ECE and SVI. Precisely, ECE was defined as carcinoma mixed with periprostatic adipose tissue or cancer tissue that extends beyond the prostate gland boundaries and included both focal and extensive ECE. The surgical margins were considered as positive if tumor cells are in contact with the ink on the specimen surface when cancer tissue was present on the inked surface of the prostate specimen.

Surgical plan in mpMRI group

All patients underwent RARP by two robotic surgeons with more than 250 RARP performed using four-arm DaVinci Si or Xi Surgical System (Intuitive Surgical, Sunnyvale, California, USA), as previous described[18]. The NS approaches were classified on patient-based level (considering 137 patients) as bilateral NS, unilateral NS, or non–NS. Indeed, the extent of NVB preservation was recorded on side-based level (considering the right and the left side of each prostate, namely 274 sides) as Grade 1, Grade 2, Grade 3 and Grade 4 according to incremental NS classification as described by Tewari et al.[11] The surgical plan to determinate the extent of NS approach both on patient-based and side-based level, was planned by surgeons in both group of patients, basing on clinical data (including PSA, clinical stage basing on DRE and TRUS, biopsy Gleason score, number and location of

positive cores) except for mpMRI findings. Subsequently, in the group of men with preoperative mpMRI, the surgical plan was re-assessed by the main surgeon after revision of mpMRI findings (both considering the size, location, PI-RADS score and suspision of ECE and/or SVI of the lesion). Thus, the final surgical plan regarding NS surgery both on patient-based and side-based level was recorded through a combination of clinical parameters and mpMRI results[11] and the change after mpMRI evaluation was recorded.

Statistical analyses

Median and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. Our statistical analyses consisted of several steps. First, we focused on the cohort of 137 patients with preoperative mpMRI. Therefore, the McNemar-Bowker test was used to compare the surgical plan regarding NS surgery, before and after revision of mpMRI results. The proportion of surgical plan change was recorded both on patient-based and side-based level. The appropriateness of surgical plan change was assessed on side-based level and was based on the presence of ECE or PSMs in the NVBs area at final pathological examination. A less radical approach, leading to a grade 1 NS, was considered appropriate in case of pT2 with negative surgical margins in the posterolateral area of prostate; similarly, a less radical approach, leading to a grade 2 NVBs preservation, was considered appropriate in case of pT2 or pT3a with negative postero-lateral surgical margins. Conversely, a more radical approach leading to a grade 2 NVB preservation was considered appropriate in case of pT2 or pT3a with negative postero-lateral surgical margins; while a more radical approach leading to a grade 3-4 NVB preservation was considered appropriate in case of pT3a/pT3b regardless surgical margins status in the posterolateral area of prostate. Finally, we compared patients submitted to mpMRI to a similar cohort of patients not submitted to mpMRI in terms of clinical and pathological characteristics. The Mann-Whitney U Test and chi-square tests were used to compare the statistical significance of differences in median and proportions between two groups, respectively. All statistical tests were performed using SPSS 20.0 for Windows.

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RESULTS

Table 1 depicts the baseline characteristics of 137 patients staged with preoperative mpMRI. Considering clinical parameters, 75 (54.7%), 43 (31.4%) and 19 (13.9%) patients were scheduled for bilateral NS, unilateral NS and non NS approach, respectively; including the knowledge of the mpMRI results, 77 (56.2%), 34 (24.8%) and 26 (19%) patients were referred to bilateral NS, unilateral NS and non NS approach, respectively (p=0.1). Similarly, on side-based level, Grade 1, 2 and 3-4 NS would have been performed in 72 (26.3%), 126 (46%) and 76 (27.7%) sides without mpMRI revision; however, Grade 1, 2 and 3-4 NS was finally performed in 79 (28.8%), 108 (39.4%) and 87 (31.8%) sides after mpMRI revision, respectively. (p=0.4; Table 2).

Table 3 depicts the surgical plan change on patient basis in patients referred to preoperative mpMRI: the initial surgical plan according to NS techniques was changed by mpMRI findings in 46.7% of men In 35 (54.7%) of cases surgery was changed to more radical approaches, resulting in a complete resection of the NVB in 18 (51.4%) and unilateral preservation of NVB in 17 (48.6%) patients. On the other hand, in 29 (45.3%) cases the NS approach was attempted (less radical approach), including 11 (37.9%) individuals, scheduled for a complete resection of NVB, receiving unilateral or bilateral NS approach and 18 (62.1%) men, scheduled for a unilateral preservation of NVB, receiving bilateral NS surgery.

Table 4 depicts the surgical plan change on side basis in patients referred to preoperative mpMRI: the mpMRI revision induced the main surgeon to change the NS surgical plan in 154 (56.2%) of sides with overall appropriateness of 75.3%, while the initial surgical plan was not changed by mpMRI findings in 120 (43.8%) of sides with appropriateness of 81.7%. In 50% of cases surgery was changed towards a more radical approaches, namely change from Grade 1 to Grade 2 or 3-4 and from Grade 2 to Grade 3-4 NS, resulting appropriate in 46/77 sides (60%). In the other half of cases, surgical plan was changed into a less radical NS approach, namely switch from Grade 2 to Grade 1 and from Grade 3-4 to Grade 2 and Grade 1 NS, resulting appropriate in 71/77 sides (92.2%, Table 4). Finally, Supplementary Table 3 depicts overall patients' characteristics of the 137 patients submitted to preoperative mpMRI compared to 166 patients not submitted to mpMRI: despite significantly higher preoperative PSA, clinical stage, biopsy Gleason score, pathologic stage

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and less frequent NS approach (all p≤0.04), patients with preoperative mpMRI revealed significant lower overall PSMs and PSMs in pT2 disease as compared with control group with no mpMRI (12.4% and 6.2% vs. 24.1% and 24.1%, respectively; all p≤0.01).

DISCUSSION

The advent of robotic technology, induced robotic surgeons to "re-design" the surgical anatomy of prostatic gland and periprostatic tissues. For example, the entity of NVB preservation is strictly related to the level of lateral incision of the periprostatica fascia, since 52% of nerves are located along the entire lateral surface of the prostate and only 48% of fibers constitute a defined bundle in the postero-lateral region[19]. This allows surgeons to significantly improve the recovery of erectile function with a range between 54% to 90% and 63% to 94% at 12 and 24-months, respectively[20]. On the other side of the coin, the area of NS is particularly predisposed to PSMs in case of dissection too close to prostatic capsule. While in open surgery the tactile feedback the tumor has been used to modify the plain of resection [21], many visual landmarks including arteries[3] and veins[11] within the multilayered periprostatic fascia[22] have been proposed with robotic approach to guide surgeons into a proper dissection. The amount of tissue remaining on the prostate to avoid a PSMs can be well controlled during the procedure, with the aim of achieving an incremental safety margin to cover the capsule and cancer[2]. As a matter of fact, the average rate of PSMs in contemporary robotic series is 15% (range: 6.5–32%), which is equivalent to the rate reported in prior open prostatectomy series but with a probable higher rate of NS procedures[21,23].

Similarly to kidney cancer, where the increasing use of abdominal imaging has led to a significant growing number of incidentally detected small renal masses[24], PSA test has anticipated the diagnosis of most PCa[25]. As a consequence, younger and healthier men are increasingly being diagnosed with localized PCa, and roughly one of third of cases shows high risk disease at presentation[25]. Despite NS approach was traditionally precluded in high risk PCa patients, since NS should not be considered a "all or non phenomenon"[21], Kumar et al.[26] suggested that a selective NS could be feasible even in high risk PCa patients with

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acceptable PSMs rates (12%, 28.8% and 35.6% in case of complete NS, partial NS and no NS approach, respectively; p<0.001). Taken together, these considerations imply the importance of accurate preoperative selection of ideal candidates to NS surgery.

To overcome the limitation of clinical parameters to predict ECE at final pathology, intra-operative frozen section of posterolateral aspects of prostate gland (NeufoSAFE approach[27]) has been proposed in order to reduce the PSMs rates and increase the NVB preservation.

In recent years, the increasing use of mpMRI has led to an improvement in tumor evaluation, with better comprehension of the prostate and cancer anatomy and its relationship with periprostatic fascia. Moreover, functional imaging (DWI and DCE) and the use of higher field strengths (3T) found to improve sensitivity for both ECE and SVI.

Therefore, we aimed to investigate the clinical implication of mpMRI to properly select ideal candidates to NS surgery. Several findings are noteworthy in our study. Firstly, mpMRI scan has been changed the clinical stage in 55% of patients referred to preoperative mpMRI, leading to overall upstaging in 56 (40.9%) of cases, both considering cT1 (67.5%) and cT2 (32.9%) disease. Interestingly, 40% of patients presumed harboring T3 disease at DRE and TRUS, revealed an organ confined disease at mpMRI (Supplementary Table 1). Secondly, the mpMRI proved to be a reliable tool for PCa staging, since it correctly predicted the pathologic stage in 70% of cases. Precisely, the concordance between mpMRI results and pathologic stage was 85.1%, 90.9% and 100% in patients harbouring a pT2, pT3a and pT3b disease, respectively (Supplementary Table 2). Hence, these results confirm the essential role of mpMRI in local staging PCa by improving the prediction of ECE and SVI, as previous reported[8,28,29]. Thirdly, despite recent studies suggest that mpMRI can change the clinical approach regarding preservation or resection of NVBs during RARP in almost one out three individuals [9,12,13,30], in our cohort the surgical plan was changed after mpMRI revision, in 64 out 137 patients (46.7%) and in 154 out 274 sides (56.2%). Accordingly to previous reports[9,16], the surgical plan change results equally assigned between the direction of more radical and less radical approach on patient-based (54.7% vs. 45.3%) and on side-based levels (50% vs. 50%), with safe results in terms of PSMs. In fact, the surgical plan change after mpMRI results review, induced surgeon to preserve more neuronal tissue without increased risk of PSMs, since PSMs rate in the

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postero-lateral region resulted 5.1%. Finally, since NS surgery should be tailored not only to PCa patients but also to specific anatomy of tumor within the prostate, as well as the concept of incremental NS better depicts the ability to modulate the grade of NVB preservation within each sides of prostate glands during lateral dissection, we aimed to assess the entity of surgical plan change induced by mpMRI and the relative appropriateness, considering the grade of NS dissection on side-based level. Overall, in 77 out 154 sides (50%) the mpMRI induced surgeon toward less radical grade of NS, resulting into appropriate surgical plan change in 92.2% of cases. While when the surgical plan was changed into direction to more radical approach in the remnant half of cases, the appropriateness was 60%. The suboptimal value of appropriateness in case of high grade of NVB resection, as previous reported[13], could be explained with a significant upstaging (up to 40.9%; Supplementary Table 1) of clinical stage by using mp-MRI, favoring a less conservative NS surgery even in case of pathological confirmed organ confined disease with negative surgical margins. Moreover, in a considerable number of patients mp-MRI showed an organ confined disease with no ECE or was completely negative for significant lesions, while the final pathology revealed extraprostatic disease in 13.4% and 14.3%, respectively (Supplementary Table 2). This could be explained with the poor positive predictive value of mp-MRI on predicting the presence of microscopic ECE. Thus, the surgeon could be induced to choose a plane of dissection too close to prostatic capsule, resulting in PSMs. However, taking into account these consideration, in case of a lesion detected at MRI and located closed to prostatic capsule (with no evidence of ECE), we performed a Grade 2 NS instead Grade 1 NS, in order to leave a fine amount of periprostatic fascia to cover the lesion aimed to reduce PSMs in case of focal extraprostatic extension at final pathology.

Surprisingly, when the surgical plan was changed into direction of highest grade of preservation (Grade 1 NS), the appropriateness increased: the surgical plan change from Grade 3-4 to Grade 1 NS and from Grade 2 to Grade 1 NS resulted appropriate in 80% and 97.4% of cases, respectively, suggesting that NS surgery could be safety performed without a relative higher risk of failure due to oncologic outcomes since in only 1 (1.3%) side referred to Grade 1 NS approach resulted positive surgical margins at level of NVB area.

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Accordingly, Rud et al.[12] showed in a prospective randomized trial, how the preoperative use of mpMRI could reduce the PSMs rates in stage cT1 PCa (16% in mpMRI group vs. 27% in non mpMRI group, p=0.0035), mainly due to excellent tumour visualization that may have prevented dissection too close to the index tumor. Moreover Petralia et al.[10] confirmed overall reduction of PSMs from 18% to 7% in patients referred to preoperative mpMRI and intraoperative frozen sections directed to the site of the index lesion. Our results, are in line with these evidences: despite the absence of randomization, the rates of overall PSMs was significantly lower in men with preoperative mpMRI as compared to those reported in the control group with no preoperative mpMRI (12.4% vs. 24.1%, p=0.01), although individuals staged with mpMRI had higher clinical and pathological stage and were submitted to NS approach more frequently (Supplementary Table 3). Moreover, the postero-lateral PSMs was lower in mpMRI group as compared to control group with no MRI after stratifying according to Grade of NS surgery, despite no statistical significance between two groups (1.3% vs. 4.7% in Grade 1 NS and 2.8% vs. 13,8% in Grade 2 NS; p=0.4; Supplementary Table 3). As consequence, mpMRI has given support to a novel concept of risk-stratified approach to NS[11], that allows more patients the opportunity to undergo NS while achieving cancer control by maintaining excellent PSMs rates. Indeed, preoperative mpMRI can improve the safety of NS approach by tailoring the side by side approach to the nerves[9,12,13].

Despite several strengths, our study is not devoid of limitations. First, it consists of two centres cohort of patients. Thus, despite well standardized RARP procedures and pathologic reports within each centre, different surgeon's attitude with respect of NS surgery and different experience in robotic procedures, as well as discordance in pathologic evaluation could have affected our results. Indeed, despite our series represent a picture of PCa treatment in two high volume European referral centres, our findings may not be representative of the experience at other centres.

Second, despite prospective design of study, the number of patients included is limited. Third, patients within two centres were submitted to different setting of MRI scans (namely, 1.5T and 3T MRI); that could implicate different diagnostic accuracy on prediction of ECE among patients. However, each 1.5T MRI was performed with standard 8-channel pelvic phased-array surface coil combined with a disposable endorectal coil. Despite this

limitation each MRI exams was carried out with functional acquisitions including DWI and DCE, suggesting a promising value to guide robotic surgeons with regards of NS surgery. Moreover, we analysed results concerning surgical plan change and appropriateness considering patients referred to 1.5T MRI and endorectal coil compared to those referred to 3.0T MRI and no significant difference was found between two groups.

CONCLUSIONS

The optimal accuracy of mpMRI in the definition of the tumor's anatomy renders the mpMRI an essential tool to guide NVB surgical management, thus inducing robotic surgeons to change the previous surgical plan in almost half of individuals and better tailoring the surgery. Our results suggest that mpMRI improves the oncologic safety of NS RARP and significantly reduced the overall PSMs compared to patients not submitted to preoperative mpMRI.

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Abbreviations

mpMRI: multiparametric magnetic resonance imaging

NS: nerve sparing surgery

PCa: prostate cancer

RARP: robot assisted radical prostatectomy

ECE: extracapsular extension

SVI: seminal vescicle invasion

PSMs: positive surgical margins

NVBs: neurovascular bundles

PSA: prostate specific antigen

DRE: digital rectal examination

TRUS: transrectal ultrasound

RP: radical prostatectomy

Table 1. Overall patients' characteristics (n= 137)

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Variable	**Overall**
No. of patients	137 (45.2)
Age (years)	
Median	64
IQR	58-68
PSA (ng/ml)	
Median	9.7
IQR	6.19-78
Number of positive biopsy cores	
Median	4
IQR	3-7
Side of positive cores, n (%)	
Unilateral	75 (54.7)
Bilateral	62 (45.3)
Clinical stage (%) basing on DRE and/or TRUS, n (%)	
T1	46 (33.6)
T2	76 (55.5)
T3	15 (10.9)
D'Amico Risk Group, n (%)	
Low	25 (18.2)
Intermediate	77 (56.2)
High	35 (25.5)
Gleason Grade group, n (%)	
1	29 (21.2)
2	47 (34.3)
3	32 (23.4)
4	16 (11.7)

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5	13 (9.5)
mpMRI results, n (%)	
Negative	28 (20.4)
Organ confined lesion (No ECE)	67 (48.9)
ECE	33 (24.1)
SVI	9 (6.6)
PI-RADS -v2, n (%)	
1-2	28 (20.4)
3	46 (33.6)
4	45 (32.8)
5	18 (13.1)
Pathologic Gleason Score, n (%)	
<7	19 (13.9)
7	87 (63.5)
8-10	31 (22.6)
Pathologic stage, n (%)	
pT2	81 (59.1)
pT3a	43 (31.4)
pT3b	13 (9.5)
Surgical margin status, n (%)	
Negative	120 (87.6)
Positive	17 (12.4)
Positive surgical margins according to pathologic stage, n (%)	
pT2	5 (6.2)
pT3a	9 (20.9)
pT3b	3 (23.1)

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Site of positive surgical margin, n (%)	
Postero-lateral	7 (5.1)
Apical-anterior	8 (5.9)
Basal-bladder neck	1 (0.7)
Multiple	1 (0.7)
Positive postero-lateral surgical margins according to Tewari et al.[11] (side- based), n (%)	
Grade 1	1 (1.3)
Grade 2	3 (2.8)
Grade 3-4	4 (4.6)
Treating centre, n (%)	
Sant'Orsola-Malpighi Hospital (Bologna, Italy)	80 (58.4)
OLV Hospital (Aalst, Belgium)	57 (41.6)

PSA: prostate specific antigen; IQR: interquartile range; DRE: digital rectal examination; TRUS: trasrectal ultrasound; mpMRI: multiparametric magnetic resonance imaging; ECE: exacapsular extension; SVI: seminal vescicles invasion; PI-RADS-v2: Prostate imaging reporting and data system version 2

Table 2. Nerve sparing technique both on patient based level and side based level before and after mpMRI revision in patients referred to preoperative mpMRI (n=137)

Variable	Before mpMRI revision	After mpMRI revision	*P value*
Nerve sparing technique (patient-based), n (%)			
Not performed	19 (13.9)	26 (19)	0.1
Unilateral	43 (31.4)	34 (24.8)	
Bilateral	75 (54.7)	77 (56.2)	
Nerve sparing approach according to Tewari et al.[11] (side-based), n (%)			
Grade 1	72 (26.3)	79 (28.8)	0.4
Grade 2	126 (46)	108 (39.4)	
Grade 3-4	76 (27.7)	87 (31.8)	
mpMRI: multiparametric resonance imaging			

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Table 3. Surgical plan change on a patient based analysis in patients referred to preoperative mpMRI (n=137)

Without surgical plan change	**73 (53.3%)**
With surgical plan change	**64 (46.7%)**
More radical approach	**35 (54.7%)**
-Bilateral NS→ No NS	8 (22.8%)
-Bilateral NS→ Unilateral NS	17 (48.6%)
-Unilateral NS→ No NS	10 (28.6%)
Less radical approach	**29 (45.3%)**
-No NS → Unilateral NS	2 (6.9%)
-No NS→ Bilateral NS	9 (31%)
-Unilateral NS → Bilateral NS	18 (62.1%)
NS: nerve sparing	

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Table 4. Surgical plan change and relative appropriateness on side based analysis in patients referred to preoperative mpMRI (n=137)

	Number	Appropriateness
Without intraoperative nerve sparing plan change	**120 (43.8%)**	**98/120 (81.7%)**
With intraoperative nerve sparing plan change	**154 (56.2%)**	**116/154 (75.3%)**
More radical approach	**77 (50%)**	**46/77 (60%)**
-Grade* 1→ Grade2	28 (36.4%)	26/28 (92.8%)
-Grade 1→ Grade 3-4	14 (18.2%)	4/14 (28.6%)
-Grade 2→ Grade 3-4	35 (45.4%)	16/35 (45.7%)
Less radical approach	**77 (50%)**	**71/77 (92.2%)**
-Grade 2→ Grade 1	39 (50.6%)	38/39 (97.4%)
-Grade 3-4→ Grade 2	28 (36.4%)	25/28 (89.3%)
-Grade 3-4→ Grade 1	10 (13%)	8/10 (80%)

* Grade of nerve sparing according to the classification proposed by Tewari et al. [11]

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Supplementary Table 1. Re-assessment of clinical stage after mp-MRI study in patients referred to preoperative mpMRI (n=137)

Clinical stage (DRE and TRUS)	**Clinical stage (mp-MRI)**			
	Negative (cT1)	**Organ confined disease (T2)**	**ECE (T3a)**	**SVI T3b)**
cT1, n (%)	15 (32.6%)	22 (47.8%)	6 (13%)	3 (6.5%)
cT2, n (%)	12 (15.8%)	39 (51.3%)	21 (27.6%)	4 (5.3%)
cT3, n (%)	1 (6.7%)	6 (40%)	6 (40%)	2 (12.3%)

DRE: digital rectal examination; TRUS: transrectal ultrasound imaging; mp-MRI: multiparametric magnetic resonance imaging; ECE: extracapsular extention; SVI: seminal vesicle invasion

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Supplementary Table 2. Re-assessment of preoperative clinical stage and positive surgical margins based on mp-MRI after pathologic revision in patients referred to preoperative mpMRI (n=137)

Clinical stage (mp-MRI)	Pathologic stage			PSMs
	pT2	pT3a	pT3b-pT4	
Negative, n (%)	24 (85.7%)	4 (14.3%)	0 (-)	2 (7.1)
Organ confined disease (T2), n (%)	57 (85.1%)	9 (13.4%)	1 (1.5%)	7 (10.4)
ECE (T3a), n (%)	0 (-)	30 (90.9%)	3 (9.1%)	6 (18.2)
SVI (T3b), n (%)	0 (-)	0 (-)	9 (100%)	2 (22.2)
mp-MRI: multiparametric magnetic resonance imaging; ECE: extracapsular extension; SVI: seminal vesicle invasion; PSMs: positive surgical margins				

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Supplementary Table 3. Overall patients' characteristics after stratifying according to preoperative use of mpMRI (mpMRI group vs. no mpMRI group; n= 303)

Variable	**mpMRI group**	**No mpMRI group**	**P value**
No. of patients	137 (45.2)	166 (54.8)	-
Age (years)			
Median	64	65	0.09
IQR	58-68	59-69	
PSA (ng/ml)			
Median	9.7	6	<0.01
IQR	6.19-78	5-8.4	
Number of positive biopsy cores			
Median	4	4	0.08
IQR	3-7	2-6	
Side of positive cores, n (%)			
Unilateral	75 (54.7)	94 (56.6)	0.7
Bilateral	62 (45.3)	72 (43.4)	
Clinical stage (%) basing on DRE and/or TRUS, n (%)			
T1	46 (33.6)	119 (71.7)	<0.01
T2	76 (55.5)	47 (28.3)	
T3	15 (10.9)	0 (0)	
D'Amico Risk Group, n (%)			
Low	25 (18.2)	57 (34.3)	0.004
Intermediate	77 (56.2)	77 (46.4)	
High	35 (25.5)	32 (19.3)	
Gleason Grade group, n (%)			
1	29 (21.2)	53 (31.9)	0.04
2	47 (34.3)	61 (36.7)	
3	32 (23.4)	26 (15.7)	

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4	16 (11.7)	18 (10.8)	
5	13 (9.5)	6 (3.6)	
mpMRI results, n (%)			
Negative	28 (20.4)	-	-
Organ confined lesion (No ECE)	67 (48.9)		
ECE	33 (24.1)		
SVI	9 (6.6)		
PI-RADS -v2, n (%)			
1-2	28 (20.4)	-	-
3	46 (33.6)		
4	45 (32.8)		
5	18 (13.1)		
Nerve sparing technique (patient-based), n (%)			
Not performed	26 (19)	64 (38.6)	0.001
Unilateral	34 (24.8)	32 (19.3)	
Bilateral	77 (56.2)	70 (42.2)	
Nerve sparing approach according to Tewari et al.11 (side-based), n (%)			
Grade 1	79 (28.8)	85 (25.6)	0.01
Grade 2	108 (39.4)	87 (26.2)	
Grade 3-4	87 (31.8)	160 (48.2)	
Pathologic Gleason Score, n (%)			
<7	19 (13.9)	21 (12.7)	0.8
7	87 (63.5)	113 (68.1)	
8-10	31 (22.6)	32 (19.3)	
Pathologic stage, n (%)			
pT2	81 (59.1)	137 (83)	<0.01
pT3a	43 (31.4)	25 (15.2)	

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pT3b	13 (9.5)	3 (1.8)	
Surgical margin status, n (%)			
Negative	120 (87.6)	126 (75.9)	0.01
Positive	17 (12.4)	40 (24.1)	
Positive surgical margins according to pathologic stage, n (%)			
pT2	5 (6.2)	33 (24.1)	0.001
pT3a	9 (20.9)	5 (20)	0.9
pT3b	3 (23.1)	1 (33.3)	0.7
Site of positive surgical margin, n (%)			
Postero-lateral	7 (5.1)	15 (9)	0.08
Apical-anterior	8 (5.9)	14 (8.4)	
Basal-bladder neck	1 (0.7)	4 (2.4)	
Multiple	1 (0.7)	7 (4.2)	
Positive postero-lateral surgical margins according to Tewari et al.[11] (side- based), n (%)			
Grade 1	1 (1.3)	4 (4.7)	0.4
Grade 2	3 (2.8)	12 (13.8)	
Grade 3-4	4 (4.6)	8 (5)	
Treating centre, n (%)			
Sant'Orsola-Malpighi Hospital (Bologna, Italy)	80 (58.4)	90 (54.2)	0.5
OLV Hospital (Aalst, Belgium)	57 (41.6)	76 (45.8)	

PSA: prostate specific antigen; IQR: interquartile range; DRE: digital rectal examination; TRUS: trasrectal ultrasound; mpMRI: multiparametric magnetic resonance imaging; ECE: exacapsular extension; SVI: seminal vescicles invasion; PI-RADS-v2: Prostate imaging reporting and data system version 2