



# Impact of Magnetic Resonance Imaging on Prostate Cancer Staging and European Association of Urology Risk Classification

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<b>OBJECTIVE</b>	To investigate the impact of magnetic resonance imaging (MRI) information on clinical staging, risk stratification, and treatment recommendations for prostate cancer (PCa) according to the European Association of Urology (EAU) guidelines.
<b>METHODS</b>	We performed a single-center analysis of 180 men with PCa, undergoing clinical staging by digital rectal examination (DRE) as well as MRI before their robot-assisted radical prostatectomy. Patients were stratified according to the EAU guidelines into 4 well-defined risk categories, based on their clinical T-stage assessed by either DRE or MRI. Descriptive statistics of categorical variables are shown as frequencies and proportions. Differences between both scenarios (DRE- vs MRI-staged) were analyzed using a paired-samples sign test.
<b>RESULTS</b>	Use of MRI information instead of DRE information leads to significant upstaging of clinical T-stage (33%) and EAU risk grouping (31%). When comparing these results with the pathologic T-stage, MRI showed a higher sensitivity than DRE to detect nonorgan-confined PCa (59% vs 41%; $P < .01$ ). In contrast, the specificity of MRI was lower than DRE (69% vs 95%; $P < .01$ ). Incorporation of MRI-based instead of DRE-based staging in the treatment decision process would alter the surgical treatment strategy in 49/180 patients (27%).
<b>CONCLUSION</b>	The incorporation of MRI information substantially affects the treatment choice in PCa patients as compared to using the current available EAU guidelines based on DRE information. More specifically, treatment intensification would be recommended in 1 out of 4 patients. UROLOGY 130: 113–119, 2019. © 2019 Elsevier Inc.

Prostate cancer (PCa) is the most common nonskin malignancy and an important cause of cancer-related mortality in men in industrialized countries worldwide.<sup>1</sup> Historically, digital rectal examination (DRE) has been the principal method of examination to locally stage malignancies of the prostate. Multiple risk

stratification models have been designed to predict the risk of PCa mortality, 5-year progression-free survival, biochemical recurrence-free survival, the risk of positive margins, nonorgan-confined disease, seminal vesicle invasion, and lymph node invasion.<sup>2–4</sup> All these stratification models combine the prostate-specific antigen (PSA) blood value and Gleason score of the prostate biopsy with clinical staging by DRE to get a more accurate prediction. However, DRE is generally believed to be a rather subjective test with potential interobserver variability and is at risk to underestimate the extent of anteriorly located tumors.<sup>5,6</sup>

In the last decade, multiparametric magnetic resonance imaging (mpMRI) of the prostate has become an important diagnostic tool for local staging in PCa. mpMRI offers superior soft tissue contrast and depiction of the zonal anatomy of the prostate. The Prostate Imaging Reporting and Data System (PI-RADS) was developed to promote global standardization in the acquisition, interpretation, and reporting of prostate mpMRI examination and was

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updated in 2015 (PI-RADS v2) based on expert consensus.<sup>7</sup> Under PI-RADS v2, mpMRI includes the combination of high-resolution T2-weighted images assessing the prostate anatomy and at least two functional MRI techniques. Given that dynamic contrast-enhanced (DCE) MRI has a secondary role to T2-weighted MRI and diffusion-weighted imaging (DWI), biparametric MRI (T2-weighted + DWI) (bpMRI) is currently suggested as a further improvement to PI-RADS v2.<sup>8</sup>

The recommended use of mpMRI during the diagnostic work-up of patients with PCa varies slightly between different international guideline organizations.<sup>9</sup> Today, the role of mpMRI in staging procedures has not entirely been clarified yet. However, there is a gradual trend to implement mpMRI information into the therapeutic decision process.

The aim of this study is to quantify the impact of using bpMRI information for risk stratification and therapeutic decision making instead of using the current standard DRE-based guidelines.

## PATIENTS AND METHODS

### Patients

This study was approved by the institutional ethical review board of the University Hospitals Leuven (S61308). In this single-institution study, patient charts were reviewed for patients with histologically proven PCa who were treated with a robot-assisted radical prostatectomy (RARP) between April 2016 and December 2017. Patients were excluded for data analysis if they had no registered DRE or if no bpMRI had been performed or evaluated in our center (Fig. 1). A total of 180 patients met these criteria. The following patient characteristics were retrospectively extracted from the medical files and included for analyses: age, clinical T-stage by DRE, clinical T-stage by MRI

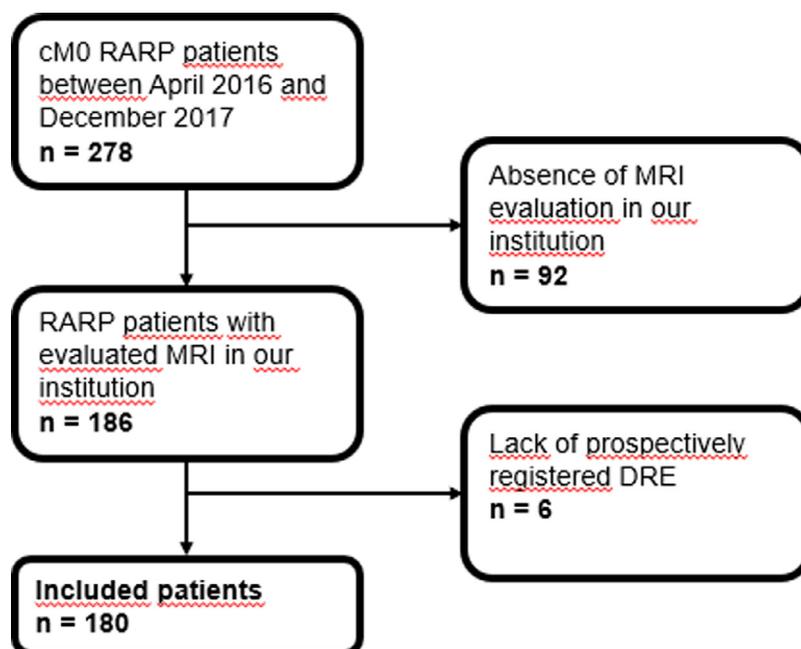
evaluation, initial PSA (iPSA), International Society of Urological Pathology (ISUP) grade group on biopsy, percentage of positive biopsy cores, preoperative erectile function state, pathologic T-stage, and ISUP grade group on final RARP specimen.

### MRI Acquisition and Interpretation

MRI was performed on a 1.5T magnet (Aera; Siemens Medical Systems, Erlangen, Germany). Axial, coronal and sagittal T2-weighted MRI, axial T1-weighted MRI and axial DWI, covering the prostate gland, seminal vesicles, and the pelvis up to the aortic bifurcation, were acquired. All MRI examinations were evaluated by 1 of 4 urologists experienced in prostate imaging. Images were evaluated on a digital workstation (Impax; Agfa, Mortsel, Belgium). The analysis of the diffusion-weighted images (apparent diffusion coefficient) was performed using an in-house developed software package.<sup>10–13</sup> Local staging was performed based on features described in the literature.<sup>14–16</sup> Focal capsular irregularity, tumor signal intensity in the periprostatic fat, neurovascular bundle asymmetry or invasion, and obliteration of the rectoprostatic angle were considered as direct signs of extracapsular extension (ECE). Tumor localization was described according to the 16 regions standardized MRI prostate reporting scheme.<sup>17</sup>

### Clinical Examination, Surgical Procedure Pathology Reporting

Preoperative DRE was performed by a senior urologist (W.E. or S.J.) immediately before surgery and recorded in the structured operation report. The findings were classified according to the clinical Tumor, Node, Metastasis (cTNM) classification of the Union for International Cancer Control (UICC 7th/8th edition). The 8th edition of the TNM classification of malignant tumors came into effect on January 1, 2017. There are no changes in the definitions of the clinical T, N, and M categories between the 7th and 8th edition for PCa. Two surgeons specialized in RARPs completed all prostatectomies with or without pelvic lymph node dissection depending on the risk of lymph node invasion, calculated



**Figure 1.** Consort flow diagram. DRE, digital rectal exam; MRI, magnetic resonance imaging; RARP, robot-assisted radical prostatectomy.

using the Memorial Sloan Kettering Cancer Center Pre-Radical Prostatectomy Nomogram (MSKCC).<sup>18</sup>

Systematic prostate biopsies, targeted biopsies as well as prostatectomy specimens were processed in accordance with the ISUP guidelines. Pathologic evaluation was performed according to the ISUP 2014 modified grading system.<sup>19</sup> Staging was described with the pathologic TNM (pTNM) classification of the UICC 8th edition.

### Recommended Surgical Treatment

According to the European Association of Urology (EAU) guidelines, nerve-sparing surgery can be performed safely in patients with PCa without a high risk of ECE, that is, cT2c or cT3 PCa or any Gleason score >7 (ISUP grade 4 or 5) on biopsy.<sup>20</sup> Moreover, the use of externally validated nomograms predicting side-specific ECE is advised for nerve-sparing treatment decision making. In our cohort, we used the MSKCC Pre-Radical Prostatectomy Nomogram. This dynamic nomogram is continuously updated and incorporates preoperative PSA, primary biopsy Gleason grade, secondary biopsy Gleason grade, and clinical stage determined by DRE.<sup>18</sup>

### Statistical Analyses

In accordance with the EAU guidelines, patients with PCa were stratified into 4 risk categories<sup>20</sup>:

- *Low risk PCa*: Gleason score <7 (ISUP 1) and PSA <10 and cT1 or cT2a;
- *Intermediate risk PCa*: Gleason score 7 (ISUP 2 or 3) or PSA 10-20 ng/mL or stage cT2b;
- *High risk PCa*: Gleason score 8-10 (ISUP 4 or 5) or PSA >20 ng/mL or stage cT2c;
- *High risk locally advanced PCa*: any Gleason score/ISUP grade; any PSA; cT3/T4 or cN1.

All patients were classified into these risk categories using clinical staging based on either DRE or MRI information. Descriptive statistics of categorical variables are shown as frequencies and proportions. Data were analyzed using SPSS 25 for Windows (IBM Corp., Armonk, NY). Differences in risk classification between DRE-staging and MRI-staging were analyzed using a marginal homogeneity test and paired-samples sign test. Statistical difference between sensitivities or specificities to detect nonorgan-confined PCa by DRE vs MRI was calculated by applying the McNemar  $\chi^2$  test. In all analyses of differences, a statistical significance level of  $P < .05$  was used. Furthermore, the prediction of organ-confined disease, using the updated MSKCC nomogram (April 10, 2018), was calculated using clinical staging based on either DRE or MRI information and was compared for both settings using the area under the receiver operating characteristic curve. We used the core-independent MSKCC nomogram, as the core-dependent MSKCC nomogram does not handle with MRI-targeted biopsies.

## RESULTS

### Patient Characteristics

The characteristics of the 180 enrolled patients are depicted in Table 1. Median age for all patients was 65 years (range 44-76 years). According to the DRE-based clinical staging, 26% of patients were classified as cT2c or higher vs 54% when using MRI-based clinical staging ( $P < .01$ ). Data on risk group

stratification according to the EAU guidelines (low, intermediate, high, and high risk locally advanced) using either DRE or MRI are shown in Table 1. Based on DRE, 39% would be classified as high risk or high risk locally advanced PCa, while this would be 63% when using MRI ( $P < .01$ ).

### Impact of MRI on Risk Stratification

Of the 180 included patients, the EAU risk group changed in 64 (36%) patients as a result of the MRI information. Overall, 56 (31%) patients were upstaged whereas only 8 (4%) were downstaged when MRI-based clinical T-staging was performed. For patients who were classified in the intermediate risk group by DRE, up to 43% ( $n = 43$ ) are staged in a higher risk group based on MRI.

When comparing these results with the pathologic T-stage after histopathologic evaluation, MRI showed a significantly higher sensitivity than DRE to detect nonorgan-confined PCa (59% vs 41%;  $P < .01$ ; Table 2). In contrast, the specificity of MRI for predicting ECE was significantly lower than DRE (69% vs 95%;  $P < .01$ ). The accuracy to distinguish organ- from nonorgan-confined disease was 71% and 64% for the DRE-based and MRI-based strategy, respectively.

By applying the updated MSKCC nomogram (April 10, 2018) area under the curve values were calculated as 0.74 (95% confidence interval, 0.66-0.81) for DRE-based organ-confined disease prediction and as 0.73 (95% confidence interval, 0.65-0.81) for MRI-based organ-confined disease prediction (Fig. 2).

### Impact of MRI on Treatment Strategy

Radical prostatectomy and external beam radiotherapy are the most commonly used treatments with curative intent for nonmetastatic PCa.

For surgically treated patients, MRI information could influence the choice between nerve- or nonnerve-sparing surgery. In our cohort, based on the EAU guidelines, 111 patients (62%) would be eligible for nerve-sparing prostatectomy after DRE-based staging. Thirty-three of those patients (30%) had nonorgan-confined PCa (pT3/pT4) on final pathologic analysis of the prostate specimen. Based on MRI information, only 68 patients (38%) would classify as eligible for nerve-sparing surgery of whom 18 (27%) had nonorgan-confined disease. The surgical treatment strategy would be different for 49 patients (27%) in total if MRI information would be used, which in the majority of cases (46 patients; 26%) would result in less nerve-sparing surgery. Seventeen (9%) patients with a transition zone tumor would be still eligible for nerve-sparing surgery and another 17 (9%) patients with a unilateral peripheral zone tumor would still be candidate for a unilateral nerve-sparing strategy. Including the sector-based tumor information, 12 (7%) patients are selected for a total nonnerve-sparing treatment.

## DISCUSSION

Precise risk group stratification constitutes a prerequisite for establishing the optimal treatment strategy in patients with PCa. Risk stratification for PCa is primarily based on clinical staging by DRE, pretreatment PSA, and biopsy information. The purpose of this study was to evaluate the impact of MRI information on risk stratification and treatment recommendations according to the EAU guidelines.

When compared to the gold standard histopathology, a clear risk of overstaging exists when using MRI (specificity

**Table 1.** Summary of patient (*n* = 180) and treatment characteristics

Characteristic	Patients (%)	
Age in years		
Mean	65	
Range	44-76	
iPSA (ng/mL)		
<10	116 (64)	
10-20	53 (29)	
>20	11 (6)	
Percentage of positive biopsy cores*		
Median	50%	
Range	9%-100%	
Highest ISUP grade group on biopsy		
1	18 (10)	
2	83 (46)	
3	40 (22)	
4	18 (10)	
5	21 (12)	
DRE-based clinical T-stage		
Low/cT1c; cT2a	119 (66) / 86 (48); 33 (18)	
Intermediate/cT2b	15 (8) / 15 (8)	
High/cT2c; cT3a; cT3b; cT4	46 (25) / 8 (4); 28 (16); 8 (4); 2 (1)	
MRI-based clinical T-stage		
Low/cT1c; cT2a	83 (46) / 14 (8); 69 (38)	
Intermediate/cT2b	0 (0) / 0 (0)	
High/cT2c; cT3a; cT3b; cT4	97 (54) / 19 (11); 58 (32); 9 (5); 11 (6)	
Pathologic T-stage		
Organ-confined/pT2a; pT2b; pT2c	100 (56) / 9 (5); 5 (3); 86 (48)	
Nonorgan-confined/pT3a; pT3b; pT4	80 (44) / 55 (31); 23 (13); 2 (1)	
Highest ISUP grade group on RALP specimen		
1	6 (3)	
2	92 (51)	
3	40 (22)	
4	16 (9)	
5	26 (14)	
Lymph node dissection (>10 LN removed)		
Yes	114 (63)	
No	66 (37)	
Pathologic N-stage		
pNx	66 (37)	
pN0	92 (51)	
pN1	22 (12)	
DRE- and MRI-based EAU risk group stratification for biochemical recurrence of localized and locally advanced PCa		
EAU risk group	Based on DRE	Based on MRI
Low risk	8 (4)	5 (3)
Intermediate risk	101 (56)	61 (34)
High risk localized	33 (18)	36 (20)
High risk locally advanced	38 (21)	78 (43)

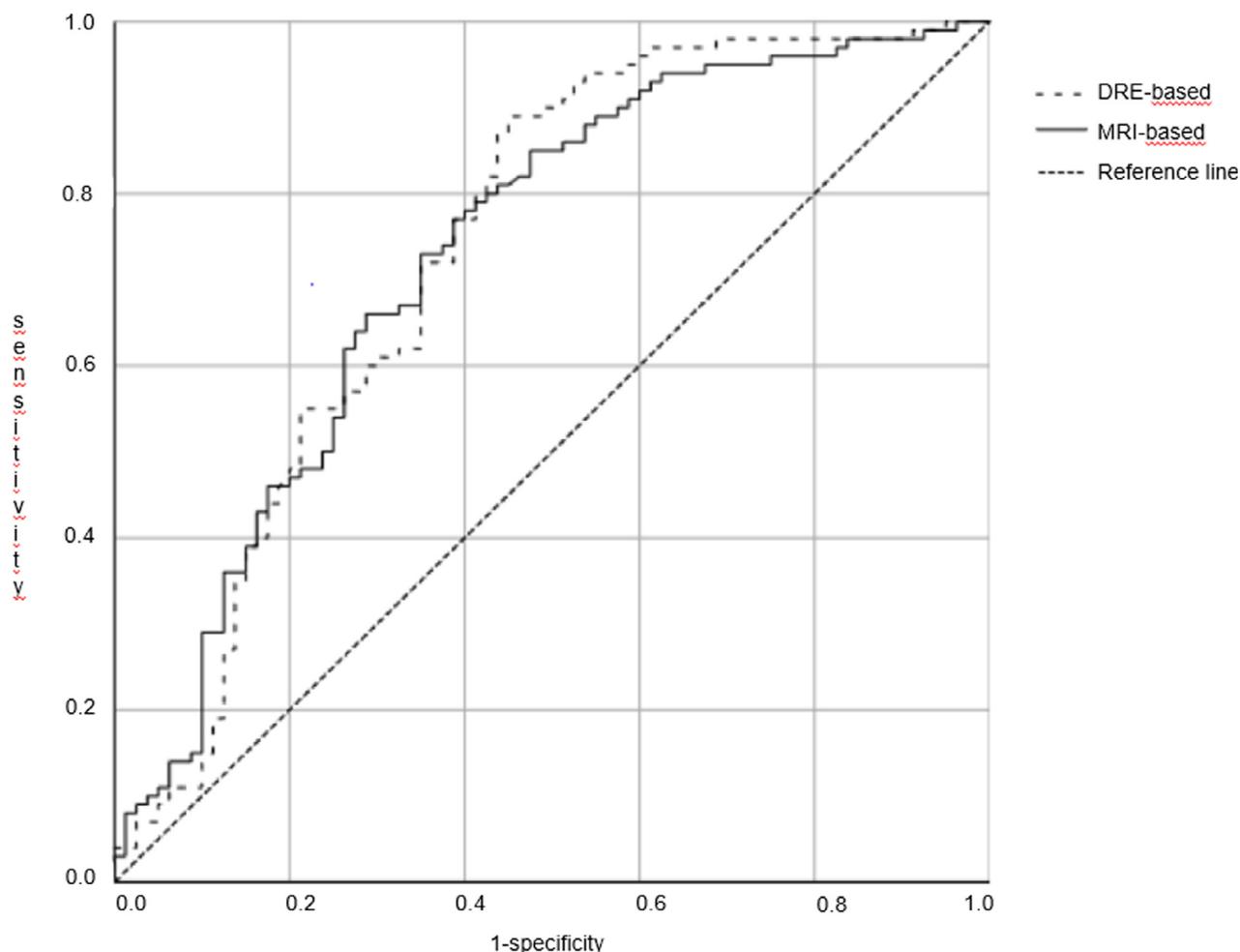
DRE, digital rectal exam; EAU, European Association of Urology; LN, lymph nodes; iPSA, initial prostate-specific antigen; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; PCa, prostate cancer; RALP, robotic-assisted laparoscopic prostatectomy.

\* There is heterogeneity in the used biopsy technique (targeted biopsies/systematic biopsies) in our patient cohort.

**Table 2.** Comparison of DRE-based and mpMRI-based clinical T-stage with pathologic T-stage (pT-stage) regarding nonorgan-confined vs organ-confined PCa

	Stage pT2 (%) (Organ-confined; <i>n</i> = 100)	Stage pT3-4 (%) (Nonorgan-confined; <i>n</i> = 80)
Organ-confined (DRE)	95 (53)	47 (26)
Nonorgan-confined (DRE)	5 (3)	33 (18)
Organ-confined (MRI)	69 (38)	33 (18)
Nonorgan-confined (MRI)	31 (17)	47 (26)

DRE, digital rectal exam; MRI, magnetic resonance imaging.



**Figure 2.** Receiver operating characteristic curve analyses of the MSKCC nomogram predicting organ-confined disease based on DRE-based clinical T-staging (dotted line) and MRI-based clinical T-staging (solid line). DRE, digital rectal exam; MRI, magnetic resonance imaging; MSKCC, Memorial Sloan Kettering Cancer Center.

69% MRI vs 95% DRE) despite the higher chance of detecting nonorgan-confined disease (sensitivity 59% MRI vs 41% DRE). This raises the question as to how we should deal with MRI-based treatment decisions, since most previous trials investigating the most appropriate local therapy defined their risk groups based on DRE.

Our study showed a high rate of recommended treatment intensification, when MRI information was used for risk stratification. Especially for patients with intermediate risk PCa staged by DRE, the use of MRI information for staging can have a large impact on the recommended treatment decision since ~40% of these patients would be upstaged. In our study, the final treatment option should be intensified in about 1 out of 4 patients if clinical staging of the tumor determined by MRI instead of DRE is taken into account. This phenomenon is described as the "Will Rogers phenomenon," which in cancer describes an artificial change in the stage of a cancer due to either a change in the staging system itself or a change in the used tumor detection technology.

While the use of neurovascular bundle-sparing techniques improves the chance of recovering erectile function,

it may lead to a higher risk of positive surgical margins. The current indications and contraindications for a nerve-sparing prostatectomy, according to EAU guidelines, are based on trials where patients were selected after staging by DRE.<sup>21</sup> Furthermore, also nomograms, predicting the chance of organ-confined disease are based on multiple parameters including clinical staging by DRE.<sup>18,22</sup> Our data show however that an important variation in surgical treatment decision can arise dependent on the knowledge of MRI information. Although, there is no evidence that one strategy is superior to the other for all cases.<sup>23</sup> Hence, the use of MRI information could probably lead to a more precise stratification to decide about nerve-sparing or nonnerve-sparing surgery if side-specific staging would be incorporated in risk stratification. Based on the concept of a side-specific nerve-sparing and an incremental nerve-sparing approach,<sup>24</sup> decisions about nerve-sparing surgery should be based on indications or nomograms which also incorporate the direct interrelationship between the neurovascular bundles and the foci of PCa.<sup>25</sup> The incorporation of MRI information could play a crucial role in the development of these tools.<sup>26</sup>

Taking our results into account, incorporation of mpMRI information into the current stratification models substantially affects EAU risk stratification in PCa patients which may lead to overstaging and hence overtreatment. There is thus a need for updated MRI-based stratification tools and treatment guidelines to avoid overtreatment. Currently, a DRE-based assessment supplemented by MRI information, especially for anterior located, transitional zone tumors which can be difficult to detect by DRE, seems to be the most pragmatic approach for clinical T-staging of PCa tumors. Furthermore, based on our analysis, continuous prediction methods, such as nomograms, are more robust than traditional risk group stratification. Prediction models calculate a balanced prediction based on multiple variables instead of a strict interpretation of each variable independently, where an alternation of one variable could have a large impact on the risk group classification.

Our current study has several limitations. First, a major limitation is its retrospective nature. This study merely evaluates the results of our current diagnostic approaches and their effects on treatment decisions. A prospective cross-sectional study is needed to truly determine superiority of one staging strategy over the other. Second, the MRIs were read by different urologists as part of the clinical routine, making results susceptible to interobserver variability. Nevertheless, the radiology workflow in this single-institution series is representative of the majority of clinical practices in the Western world. In our study, MRI was performed using a 1.5T magnet without the use of an endorectal coil, in accordance to the PI-RADS v2 guidelines, which support the use of both 1.5T and 3T MRI scans. Signal-to-noise and contrast-to-noise ratios differ between 1.5T and 3.0T mpMRI, with 3.0T scans providing better signal-to-noise and contrast-to-noise ratios.<sup>27</sup> Nevertheless, recent prospective studies have demonstrated comparable diagnostic accuracy of an optimized 1.5T bpMRI without endorectal coil compared to 3.0T mpMRI.<sup>28,29</sup> Finally, also DRE results are highly susceptible to interobserver variability.<sup>30</sup> In our study, DRE was always performed by one of the senior urologists (S.J. or W.E.) before surgery and prospectively recorded in our structured operation report.

In conclusion, our study demonstrated that there is an important discrepancy between clinical T-staging by DRE and clinical T-staging by MRI, which has a substantial influence on risk group stratification. This switch of risk group has important implications on the corresponding treatment strategy for a large number of patients, with about 1 out of 4 patients requiring intensified surgical. Future evaluation of the added value of the incorporation of MRI information in predictive tools and nomograms is necessary to develop a contemporary, updated risk stratification model based on the current available investigations during the standard work-up of patients with PCa.

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