

Clinical-Prostate cancer

# The impact of local staging of prostate cancer determined on MRI or DRE at time of radical prostatectomy on progression-free survival: A Will Rogers phenomenon

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## Abstract

**Introduction:** We aimed to test whether the current practice of using mpMRI stage might lead to a Will Rogers phenomenon with a stage migration compared to DRE in men undergoing radical prostatectomy.

**Material and methods:** A total of 572 consecutive patients who underwent radical prostatectomy at a single institution (2007–2017) were included. Clinical stage using digital rectal examination was determined on table by the operating surgeon; mpMRI and pathological stage were recorded after tumor board review. Progression-free survival (PFS) was defined as no rising PSA, no adjuvant/salvage treatment, and no metastases or mortality. PFS was compared between groups and a model incorporating mpMRI into the EAU risk groups was created.

**Results:** Median age was 63 years (IQR 58.5–67) and median PSA was 8.9 ng/ml (IQR 6.5–13.2). Using DRE stage, 20% were NCCN low risk, 43% were intermediate, and 37% high. Median follow-up was 48 months (IQR 22–73). Estimated PFS at 1, 3, and 5 years was 75%, 59%, and 54%, respectively. When comparing PFS between DRE and mpMRI stages, patients deemed T1 ( $P < 0.01$ ) or T3 ( $P = 0.03$ ) by mpMRI showed better outcomes than patients staged T1 or T3 by DRE. On univariable analysis lower risk for failure was seen for MRI T1 disease (HR 0.10 95% CI 0.01–0.73,  $P = 0.02$ ) or MRI T3 (HR 0.70, CI 0.51–0.97,  $P = 0.03$ ). On multivariable analysis, only MRI T1 remained a significant predictor (HR 0.08, 95% CI 0.01–0.59,  $P = 0.01$ ). The subsequent, modified EAU risk model using both DRE and mpMRI performed significantly better than the DRE model.

**Conclusion:** PFS based on mpMRI is not the same as DRE staging. Current risk groups which use DRE should be used with caution in whom local stage is based on mpMRI. Our modified EAU-risk categories can provide greater accuracy. © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

**Keywords:** Prostate cancer; Magnetic resonance imaging; Radical prostatectomy; Will Rogers phenomenon; Stage migration

**Abbreviations:** AIC, Akaike information criterion; DRE, digital rectal examination; EAU, European association of Urology; mpMRI, multiparametric magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PFS, progression-free survival; PSA, prostate-specific antigen

## 1. Introduction

Current preoperative risk classification of prostate cancer uses nomograms such as Partin tables, D'Amico criteria or European Association of Urology (EAU) risk groups which were developed and validated using clinical stage

assigned by digital rectal examination (DRE) [1–3]. Risk migration from improved diagnostics has been observed when the Gleason scoring system was updated in 2005 [4,5]. Multiparametric magnetic resonance imaging (mpMRI) has been validated as the gold standard test prior to prostate biopsies, however its use in assigning t-stage has not [6,7]. It is likely that the outcomes of patients staged by digital rectal examination are not the same as for those staged by mpMRI [8]. Often mpMRI T3 disease is reported

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based on radiological findings such as long capsular contact rather than true macroscopic extra capsular disease [6] and the increasing use of mpMRI may be leading to a stage migration of patients into a higher risk category with implications for the type of treatment offered. This apparent shift in risk represents the Will Rogers phenomenon, which is a mathematical paradox that results from moving an element from one set to another set and raises the average values of both sets. This phenomenon has already been documented from the use of mpMRI and MR-targeted biopsies [5,9].

Our aim was to test whether such a phenomenon might be occurring with respect to progression-free survival (PFS), when assigning stage based on mpMRI rather than DRE prior to radical prostatectomy.

## 2. Material and methods

### 2.1. Patients

Retrospective analysis of patients with clinically localized prostate cancer undergoing radical prostatectomy using a laparoscopic approach in a single institution from May 2007 to September 2017. All cases were primary, and no patient underwent salvage prostatectomy. Only a small minority of patients (7%) had ADT in the form of Bicalutamide prior to the surgery. However, in all cases it was a short-term treatment (<12 weeks) between the biopsy results and the date of surgery. Data were maintained in a prospectively maintained registry. Local institutional ethical exemption was granted.

### 2.2. Interventions

Prior to surgery, all patients underwent a diagnostic assessment consisting of prostate-specific antigen (PSA), DRE, prostate mpMRI, and either a trans-rectal or trans-perineal prostate biopsy. Digital rectal examination was performed and recorded by a single surgeon (MW) on table prior to placement of laparoscopic ports at time of surgery. Pre and postsurgical pathology data were available for all patients. Prostate mpMRI were carried out to PROMIS standards [7,10]. The majority of mpMRIs were performed with a 1.5T magnetic field strength, without an endorectal coil, including T1-weighted, T2-weighted sequences, diffusion-weighted imaging with corresponding apparent diffusion coefficient map, and dynamic contrast-enhanced sequences. T-stage on mpMRI was reported by the radiologist prior to the biopsy. All mpMRI scans were reviewed in dedicated multidisciplinary team meeting by an expert uro-radiologist prior to the surgery. T3a disease was described as a visible extracapsular extension of the tumor on the mpMRI. Broad capsular contact was also considered as T3a disease. Final postoperative pathology was reviewed in a routine tumor board meeting.

### 2.3. Follow-up

The postprostatectomy follow-up was standardized to include serum PSA measurement at 3, 6, and 12 months

after treatment, then every 6 months until 3 years, and then annually. According to PSA kinetics, additional imaging tests were performed, as clinically indicated. Patients underwent adjuvant/salvage treatment in cases of high-risk or locally advanced disease on pathology or those that developed biochemical failure according to recommendations from EAU guidelines.

### 2.4. Primary outcome

PFS was defined as no rise in PSA after surgery, no adjuvant/salvage treatment, and no metastases or mortality. PFS was compared between the various DRE and mpMRI stages.

### 2.5. Secondary outcomes

Our secondary outcomes included evaluation of PFS according to the final pathological stage. We also aimed to create a model incorporating the EAU risk groups [3] for PFS that incorporated mpMRI staging results. The goal was to evaluate if the new model can distinguish more precisely between low-, intermediate-, and high-risk groups for failure than the standard EAU risk groups using DRE.

### 2.6. Statistical analysis

To facilitate the comparison between clinical (DRE) and radiological (mpMRI) staging the patients were grouped and labeled in the following fashion: T1c (no nodule on DRE or no visible lesion on MRI), T2a-T2b (unilateral lesion on DRE/MRI), T2c (bilateral lesion on DRE/MRI), T3 (suspicion of extracapsular extension/seminal vesical invasion on DRE or MRI), and T4 (spread into other nearby organs on DRE or MRI). Our sample size was deemed to be sufficient for multivariable modeling in accordance with Peduzzi et al. [11]. Baseline characteristics are presented as the median (interquartile range [IQR]) or proportion, as appropriate. Kaplan–Meier estimates of time-to-event outcomes are described with 95% confidence intervals (95% CI). The log rank test was used to assess differences in Kaplan–Meier estimates. The univariable analysis and multivariable Cox regression analysis was performed for the clinical and radiological stage subgroups. In multivariable analysis staging was corrected for age, grade group and PSA. Proposed EAU risk models that incorporated mpMRI were compared using Akaike's information criterion. We used multiple imputation for missing data, which was considered missing at random. The first imputed dataset was used for calculating survival probabilities and modeling. As a sensitivity analysis we also assessed PFS according to final pathological stage. R version 3.5.3 was used for all statistical analyses (R Foundation for Statistical Computing, Vienna, Austria, mice and rms packages). All statistical tests had significance set at a *P* value of <0.05.

Table 1  
Patients baseline characteristics.

Variable	Overall population
<i>N</i> (%)	572
Age, median (IQR)	63 years (59–67)
PSA baseline, median (IQR)	9 ng/ml (7–13)
Clinical tumor stage, <i>n</i> (%)	
cT1c	287 (50)
cT2ab	141 (25)
cT2c	53 (9)
cT3	91 (16)
MRI tumor stage, <i>n</i> (%)	
cT1c	14 (2)
cT2ab	119 (21)
cT2c	65 (11)
cT3	144 (25)
Missing	230 (40)
Biopsy ISUP grade group, <i>n</i> (%)	
1	178 (31)
2	273 (48)
3	73 (13)
4	22 (4)
5	25 (4)

### 3. Results

#### 3.1. Patient characteristics

A total of 572 underwent radical prostatectomy (Table 1) in whom DRE stage was available. MpMRI staging was available in 60% (*n* = 342). Median follow-up time of 48 months (IQR 22–73). Overall actuarial PFS at 1, 3, and 5 years was 75%, 59%, and 54%, respectively.

A rising PSA was seen in 20% (*n* = 113) with PSA failure-free survival at 1, 3, and 5 years of 83%, 79%, and 76% respectively; 35% (*n* = 202) underwent adjuvant/salvage treatment with treatment-free survival at 1, 3, and 5 years of 75%, 61%, and 57%, metastasis were detected in 3% (*n* = 16) with metastasis-free survival at 1, 3, and 5 years of 97%, 96%, and 95%. About 3% of patients died during the follow-up (*n* = 17).

#### 3.2. Primary outcome

##### 3.2.1. Progression-free survival comparison between stages

In the T1c group comparison, PFS at 1, 3, and 5 years was 78% (95% CI 73–83), 65% (95% CI 59–71), and 61% (95% CI 55–67) for cases deemed T1c by DRE compared to 100% at 1 year and 94% and 3 and 5 years (95% CI 83–100) for cases deemed T1c by MRI. For unilateral disease (T2ab) the PFS at 1, 3, and 5 years was 81% (95% CI 74–88), 66% (95% CI 57–76), and 60% (95% CI 50–71) for cases deemed T2ab by DRE compared to 80% (95% CI 75–86), 68% (95% CI 62–75), and 63% (95% CI 56–71) for cases deemed T2ab by MRI. For bilateral disease (T2c) the PFS at 1, 3, and 5 years was 78% (95% CI 68–90), 60% (95% CI 47–76), and 46% (95% CI 32–68)

for cases deemed T2c by DRE compared to 85% (95% CI 79–92), 62% (95% CI 53–72), and 54% (95% CI 45–65). Finally, in the T3 comparison, PFS at 1, 3, and 5 years was 52% (95% CI 42–64), 33% (95% CI 24–46), and 27% (95% CI 18–40) for cases deemed T3 by DRE compared to 62% (95% CI 55–69), 47% (95% CI 40–55), and 42% (95% CI 35–50) for cases deemed T3 by MRI. There were no T4 cases documented on DRE or mpMRI. Statistically significant differences in PFS were seen in the T1 (*P* < 0.01) and T3 groups (*P* = 0.03) (Fig. 1).

#### 3.2.2. Univariable and multivariable analysis

Univariable and multivariable analysis were performed in a subgroup fashion (Table 2). Comparisons were made between the DRE and mpMRI stage groups. It showed that those staged as mpMRI T1c (HR 0.1 (95% CI 0.01–0.73, *P* = 0.02) or T3 (HR 0.7 (95% CI 0.51–0.97, *P* = 0.03) were at lower risk for failure compared to patients staged as T1c or T3 on DRE. After multivariable analysis correcting for age, grade group and PSA only MRI T1c remained a significant predictor for a better outcome (HR 0.08 (95% CI 0.01–0.59, *P* = 0.01). The statistical significance was not reached for other categories.

#### 3.3. Secondary outcomes

##### 3.3.1. Final pathology

The final pathology revealed T2a or T2b in 5% (*n* = 29), T2c in 48% (*n* = 277), T3a or T3b in 42% (*n* = 245), and T4 disease 1% (*n* = 8) of the patients. Fig. 2 demonstrates PFS according to final pathology stage. The Kendall–Tau correlation test was concordant in 21% of the cases for the DRE and final pathology and in 30% of the cases for MRI and final pathology indicating significant correlation (*P* < 0.001).

##### 3.3.2. Proposed risk stratification table

According to our results we modified the suggested EAU risk groups incorporating the mpMRI outcome to evaluate if the model would perform better when predicting PFS (Table 3). A total of 4 groups were created: low-risk, intermediate-risk, intermediate–high-risk, and high-risk.

The model using mpMRI classification was preferred over the DRE model (Fig. 3). For the low-risk group the PFS at 1, 3, and 5 years was 90% (95% CI 84–98), 82% (95% CI 73–92), and 78% (95% CI 68–90); for the intermediate-risk group 85% (95% CI 79–89), 67% (95% CI 60–74), and 57% (95% CI 49–66); for the intermediate–high-risk group 67% (95% CI 62–79), 55% (95% CI 46–66), and 51% (95% CI 41–63); and for the high-risk group 70% (95% CI 48–65), 38% (95% CI 30–48), and 30% (95% CI 22–41). In the 4 group mpMRI incorporating model (low-risk; intermediate-risk; intermediate–high-risk; high-risk) there was a significant

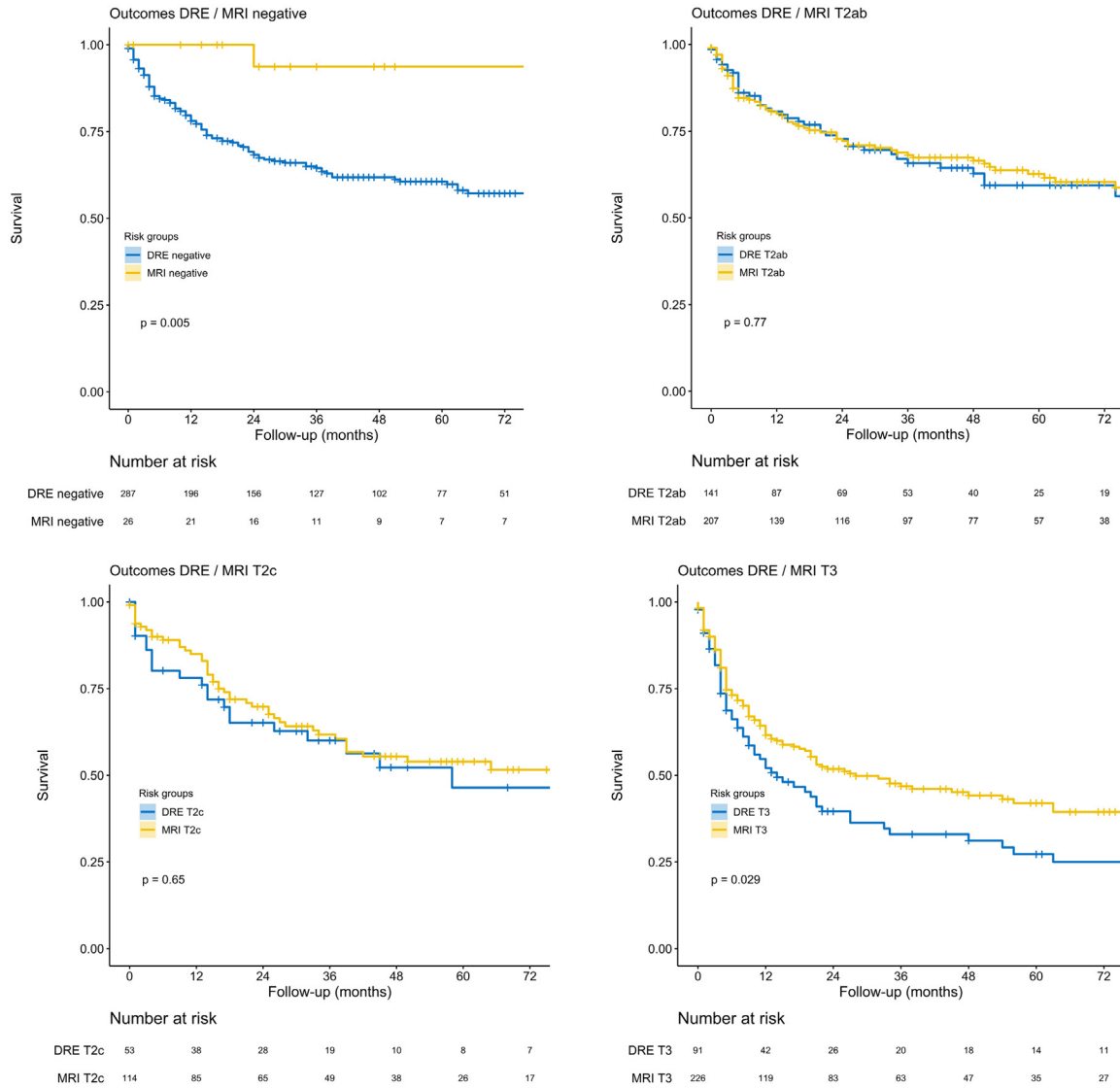


Fig. 1. Kaplan–Meier curves comparing the PFS between DRE and MRI stages.

difference between the outcomes for low-risk vs. intermediate–high-risk (HR 2.2, 95% CI 1.2–4.1,  $P = 0.02$ ), and high-risk (HR 2.9, 95% CI 1.4–5.8,  $P < 0.01$ ) groups. In the classic 3 group model with DRE staging and no mpMRI

(low-risk, intermediate-risk, high-risk), only outcomes between low-risk vs. high-risk were significant (HR 2.5, 95% CI 1.4–4.6). The models using both DRE and mpMRI outperformed DRE or mpMRI model only (lowest Akaike information criterion (AIC) value was obtained with the model using DRE and MRI (Supplementary Table 1). The C-index values were the following: 0.656 for combined model, 0.666 for MRI model and 0.653 for DRE model.

Table 2

Univariable and multivariable analysis performed in a subgroup fashion, comparing between clinical and radiological stages.

	Univariable analysis	Multivariable analysis (corrected for age, grade group, and PSA)
T1c (MRI vs. DRE)	HR 0.10 (95% CI 0.01–0.73, $P = 0.02$ )	HR 0.08 (95% CI 0.01–0.59, $P = 0.01$ )
T2ab (MRI vs. DRE)	HR 0.94 (95% CI 0.65–1.38, $P = 0.77$ )	HR 1.09 (95% CI 0.74–1.61, $P = 0.67$ )
T2c (MRI vs. DRE)	HR 0.88 (95% CI 0.53–1.47, $P = 0.63$ )	HR 1.03 (95% CI 0.61–1.74, $P = 0.90$ )
T3 (MRI vs. DRE)	HR 0.70 (95% CI 0.51–0.97, $P = 0.03$ )	HR 0.76 (95% CI 0.54–1.05, $P = 0.09$ )

#### 4. Discussion

We compared oncological outcomes between clinical DRE and radiological mpMRI staging in a cohort of patients who underwent radical prostatectomy. We found that radiological staging with mpMRI rather than DRE leads to a possible Will Rogers phenomenon due to a stage migration. At 4 years median follow-up, the patients staged as T1c or T3 with mpMRI showed improved PFS compared to patients staged as T1c or T3 on DRE. No difference in

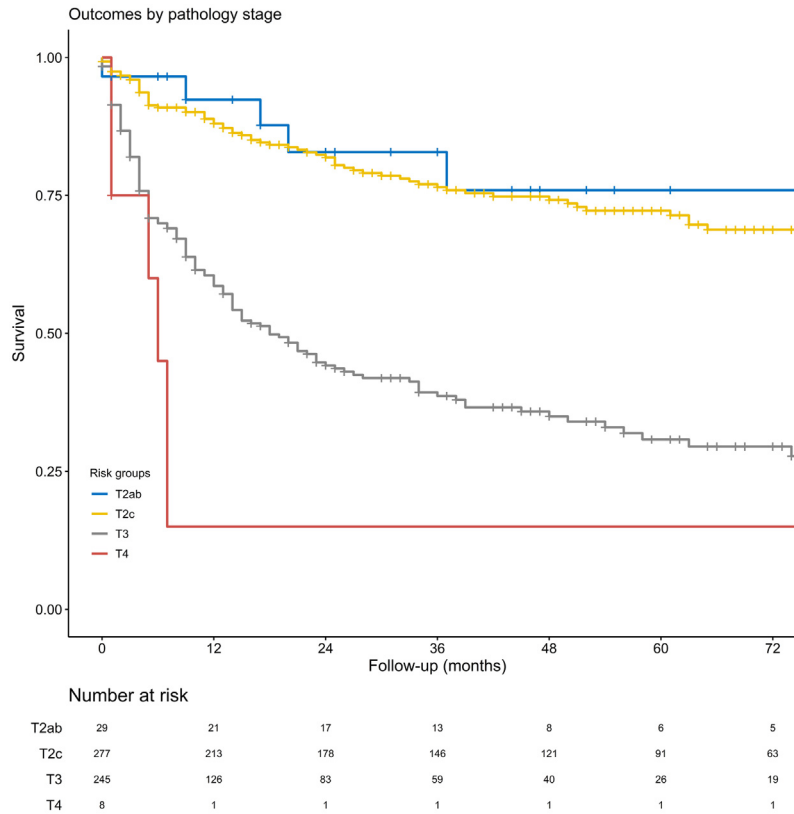


Fig. 2. Comparison of PFS according to the final pathology result.

PFS was seen in patients staged as T2 on DRE or mpMRI. Our modified EAU risk group model that incorporates mpMRI in addition to DRE appears to provide a more precise risk stratification for predicting progression than the classic EAU risk group table.

The current EAU risk groups for prostate cancer do not incorporate radiological staging and are based on Partin tables and D’Amico criteria which were originally developed and validated using clinical stage on DRE [3]. Recently there have been publications that report on the use of mpMRI stage instead of DRE but to our knowledge none have assessed its role in addition to DRE [12,13]. A recent publication by Mazonne et al. proposed a novel classification to predict biochemical recurrence based on clinical and mpMRI parameters [14]. This model based on retrospective

analysis of 2,565 patients has outperformed current available risk stratification nomograms. However, the DRE was not included in the baseline clinical parameters. Our findings confirmed the ability of DRE to predict outcomes from treatment and strongly suggest that in addition to this, incorporating mpMRI into the current EAU risk groups would lead to further improvements and increased precision.

Other existing risk prediction tools based on clinical staging in prostate cancer have already been adapted after the introduction of mpMRI and MR-targeted biopsies. For example, Gandaglia et al. developed a nomogram to predict lymph node invasion in prostate cancer when using mpMRI and MR-targeted biopsies in the initial work up [15]. Their findings confirm that the available models predicting lymph

Table 3  
Modified EAU risk groups table with added mpMRI outcome, modified DRE classification, and incorporated intermediate–high-risk group.

Low-risk	Intermediate-risk	Intermediate–high-risk	High-risk	
PSA <10 ng/ml and GS <7 (ISUP grade 1) and cT1-2ab MRI T1/2ab Localized	PSA 10–20 ng/ml or GS 7 (ISUP grade 2/3) or cT2c MRI T2c	Same as intermediate (10–20) Same intermediate (GS7 2/3) Same as intermediate MRI T3	PSA >20 ng/ml or GS >7 (ISUP grade 4/5) Same as intermediate MRI T3	any PSA any GS (any ISUP grade) cT3-4 or cN+ MRI T4 Locally advanced

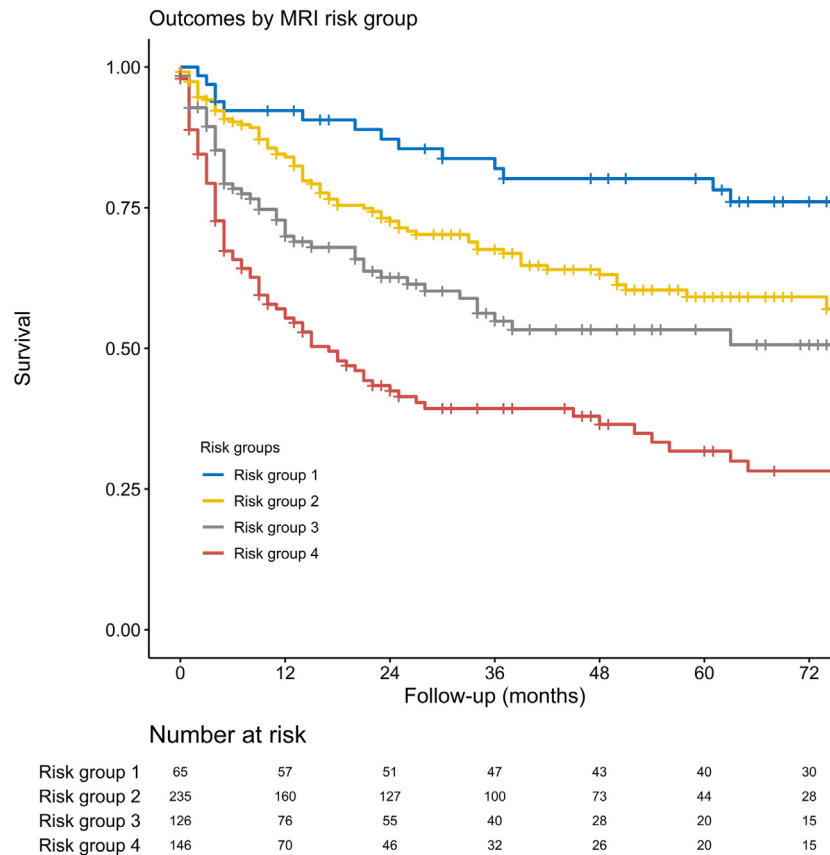


Fig. 3. PFS comparison between 4 proposed EAU risk groups (low risk, intermediate, intermediate-high, and high risk).

node invasion prior to radical prostatectomy were suboptimal when mpMRI was used.

Studies analyzing the accuracy of radiological staging show contradictory results. Gupta et al. compared mpMRI prognostic accuracy for organ confined disease and extracapsular extension and found that mpMRI had 28% higher diagnostic accuracy than the Partin tables [13]. Zhang et al. analyzed the ability of MRI to detect extracapsular extension and seminal vesicle invasion in 158 patients with clinical stage T1c cancer. In their findings, mpMRI achieved 80% accuracy in disease staging. On the contrary, a meta-analysis of almost 10,000 patients showed poor and heterogeneous sensitivity for mpMRI to detect extracapsular extension and seminal vesicle invasion [16]. Their findings were also backed up by another multicenter study with 55% of cases with locally advanced disease (pT3-4) remaining undetected by preoperative mpMRI with half of the cases falsely showing positive T3-T4 disease, with subsequent pathological examination showing organ-confined disease [17]. However, studies also show that clinical DRE staging correlates poorly with final pathology. Philip et al. in their cohort of 408 men showed that DRE under-staged 60% of men with histological diagnosis of cancer. In final pathology almost 40% of patients with normal DRE (T1c) were staged T2 or T3 [18]. Another study showed a 70% upstaging from clinical T2a disease to T2c disease in final

pathology and poor correlation for DRE to define the location and extent of the disease [19]. In summary, both diagnostic tests are not optimal for accurate preoperative staging of prostate cancer. However, mpMRI seems to perform better than clinical DRE staging.

There are some limitations to our study. First the surgeon was not blinded to the mpMRI results, thus being susceptible to verification bias in his judgment of local stage when performing the DRE. However, this is also one of the strengths, as the DRE was recorded by the same surgeon for all included cases, thus eliminating performance bias. The DRE stage was that determined on table with a fully relaxed and anaesthetized patient in the lithotomy position leading to a more thorough DRE than would be performed in the left lateral position in an awake patient in clinic. We do note though that this may have led to better performance of DRE staging. Second, most patients underwent a 1.5T mpMRI. The current evidence suggests that 3T mpMRI results in better imaging quality, especially in the diffusion-weighted imaging [20]. However, there is no evidence that it significantly impacts the diagnostic accuracy, and we would argue that it was not a significant bias in our study since each mpMRI was optimized for performance and undertaken in expert centers and was reviewed in a dedicated MDT by an expert uro-radiologist. Also, there were few negative mpMRI cases in our population. This may lead to a less precise assessment on the

differences between a negative DRE and negative mpMRI in our results. Finally, from the statistical point of view, 40% of MRI cases were missing and multiple imputation was used to correct for this. In literature, imputation up to 90% missing values seems possible and is able to give unbiased results [21]. In our view, the missing data correction here has not resulted in any significant differences in our results, although the use of a single imputed dataset might have decreased precision.

Prior to any widespread adoption external validation will be important across institutions and treatment types. A concern when redefining risk groups is that it may in turn affect the choice of the treatments offered. For example, a patient with low PSA, low volume ISUP grade 1 disease and small bilateral lesions on mpMRI, but normal DRE would previously be considered as low-risk disease. However, the new diagnostic test portrays this patient to potentially have more unfavorable disease. Should this man still be counseled for active surveillance according to the current recommendations? Conversely, a patient with T2 disease on DRE, but showing features of T3 disease on mpMRI might be offered radiotherapy only rather than being offered both prostatectomy and radiotherapy as options. Patients with nonpalpable disease but positive mpMRI and patients with mpMRI T3 disease are the most likely to be attributed to the wrong risk group using the current tools based on clinical staging.

## 5. Conclusion

There is an urgent need for recalibration of risk stratification tables for prostate cancer in the MRI-era. Current risk stratification tables were developed and validated on clinical DRE stage. Caution should be applied when substituting this with MRI stage especially when counseling patients for treatment. We have proposed an improvement upon the EAU risk groups which incorporates both DRE and MRI.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urolonc.2022.10.023>.

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