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Original article

Adding multiparametric MRI to the MSKCC and Partin nomograms for primary prostate cancer: Improving local tumor staging?

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Abstract

Introduction and objectives: As a single diagnostic modality, multiparametric MRI (mpMRI) has imperfect accuracy to detect locally advanced prostate cancer (T-stages 3-4). In this study we evaluate if combining mpMRI with preoperative nomograms (Memorial Sloan Kettering Cancer Center [MSKCC] and Partin) improves the prediction of locally advanced tumors.

Materials and methods: Preoperative mpMRI results of 430 robot-assisted radical prostatectomy patients were analyzed. MSKCC and Partin nomogram scores predicting extraprostatic growth were calculated. Logistic regression analysis was performed, combining the nomogram prediction scores with mpMRI results. The diagnostic value of the combined models was evaluated by creating receiver operator characteristics curves and comparing the area under the curve (AUC).

Results: mpMRI was a significant predictor of locally advanced disease in addition to both the MSKCC and Partin nomogram, despite its low sensitivity (45.3%). However, overall predictive accuracy increased by only 1% when mpMRI was added to the MSKCC nomogram (AUC MSKCC 0.73 vs MSKCC + mpMRI 0.74). Predictive accuracy for the Partin Tables increased 4% (AUC Partin 0.62 vs Partin + mpMRI 0.66).

Conclusion: The addition of mpMRI to the preoperative MSKCC and Partin nomograms did not increase diagnostic accuracy for the prediction of locally advanced prostate cancer.

Keywords: Prostate cancer; Multiparametric MRI; Nomogram; Staging; Locally advanced prostate cancer; Diagnostic accuracy

1. Introduction

Accurate staging of primary prostate cancer (CaP) is essential, for the distinction between organ confined cancer (T-stage 1-2) and locally advanced disease (T3-4) influences both prognosis [1] and treatment planning [2]. For instance, the presence of locally advanced disease excludes the possibility of nerve-sparing surgery (on the affected prostate lobe), as such procedure increases the risk of positive surgical margins [2−4]. Moreover, locally advanced tumors warrant the performance of a concomitant extended pelvic lymph node dissection [2,3]. Similarly, when choosing radiotherapy, the local tumor stage guides decisions on radiation dose, radiation field and adjuvant therapies [2,5].

For assessing the tumor stage, routine diagnostic parameters (i.e., digital rectal examination, serum prostate-specific antigen level, and prostate biopsy results) alone are insufficient [6]. Combining clinical parameters into *nomograms,* however, was shown to provide a more reliable prediction of locally advanced disease [7−9]. Therefore, the use of these predictive nomograms is currently

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recommended by clinical guidelines [2]. Two frequently used and externally validated nomograms include the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram [8] and the Partin tables [9].

In addition to routine diagnostics and nomograms, the use of preoperative multiparametric magnetic resonance imaging (mpMRI) is increasing. mpMRI is an imaging technique that combines different (functional) imaging sequences to improve detection and localization of malignant lesions. The technique shows promising accuracy for the detection of prostate cancer [10,11], but the assessment of the tumor stage is still imperfect. In a recent meta-analysis, the sensitivity of mpMRI for T3 tumors was 61% only (95% confidence interval [CI] 54−67%) [12].

Although mpMRI as stand-alone modality seems insufficient for accurate staging, it might still improve diagnostic accuracy in combination with other available clinical parameters. In the present study we combined mpMRI findings with the MSKCC nomogram and Partin tables to predict locally advanced disease and estimated the added diagnostic value of mpMRI for staging.

2. Patients and methods

2.1. Patients

A previously described research cohort was analyzed, consisting of 430 concurrent patients with confirmed prostate adenocarcinoma for which a robot-assisted laparoscopic radical prostatectomy (RARP) and a preoperative mpMRI was performed [13]. Patients were included between 2012 and 2016, in 3 Dutch hospitals (Amsterdam University Medical centers [VU University Medical Center], Amsterdam; Maasstad Ziekenhuis, Rotterdam; Meander Medisch Centrum, Amersfoort).

2.2. Imaging protocol and radiologic accuracy

A detailed description of the imaging protocol can be found in the previous report on the diagnostic accuracy of mpMRI in this cohort [13]. In short, 3T MRI scanners were used without endorectal coils. Per hospital, the MR images were interpreted clinically by 2 to 3 radiologists, dedicated to prostate MRI interpretation. If patients were referred to the participating centers of this study and MRI studies were already attained, no revision by the centers' own radiologists took place. The radiologic T-stage was based on the exact T-stage reported by the radiologist or based on the MRI report describing the presence or absence of extracapsular extension. Radiologic T-stage was compared to the pathologic T-stage (pT) following RARP (reference standard). Locally advanced disease (pT3-4) was present in 137 of 430 patients (31.9%), for which mpMRI had a sensitivity of 45.3% (95% CI 36.9−53.6%), specificity 75.8% (CI 70.9−80.7%), PPV 46.6% (CI 38.1−55.1%), and NPV 74.7% (CI 69.8−79.7%) [13].

2.3. Nomograms

The clinical and preoperative pathology data needed to use the MSKCC nomogram and Partin Tables were retrieved. An overview of the included parameters of both nomograms is presented in Table 1. The MSKCC risk score (%) for extracapsular extension (T3a) was calculated using the online published regression coefficients [14]; the Partin risk score (%) for extracapsular extension was based on the regression model as provided by the Partin research group [15].

2.4. Statistical analysis

Continuous variables were summarized by their medians and interquartile ranges. Categorical variables were presented as percentages. Both pathologic outcomes (pT) and mpMRI results (rT) were classified as either organ-confined disease (T0-2) or locally advanced disease (T3-4), and treated as binary variable. The significance level was set at $P < 0.05$.

Binary logistic regression analysis was performed for the MSKCC nomogram, Partin tables and mpMRI results separately (univariable analysis). The mpMRI results were then step-wise included to the logistic regression with the MSKCC nomogram as base (multivariable analysis). A similar procedure was performed for the regression with the Partin table as base. Likelihood-ratio tests were performed to analyze if the addition of mpMRI results yielded significantly increased accuracy.

Receiver operating characteristic (ROC) curves were created for the MSKCC nomogram, Partin tables and mpMRI results, as well as the combinations MSKCC + mpMRI and Partin + mpMRI (using the predicted probabilities of the multivariable analyses). The different areas under the curves (AUC) of all models were compared.

Table 1
Overview of the parameters included in the MSKCC nomogram and Partin table

Included clinical parameters	Input to the model	
	MSKCC nomogram	*Partin tables*
Preoperative PSA (ng/ml)	(continuous)	0−4.0 4.1−6.1 6.1−10.0 >10.0
Biopsy Gleason score	Primary grade >3 Secondary grade >3	2−6 3+4 4+3−8 9−10
Biopsy cores (number)	Neg. cores (continuous) Pos. cores (continuous)	*not included*
Clinical stage	T2a T2b T2c T3+	T1c T2a T2b/T2c

3. Results

Patient characteristics are displayed in Table 2. The MSKCC risk scores for extraprostatic extension ranged from 26.0% to 100% (median 64.4%). The Partin risk scores could not be calculated for patients with clinically staged T3 tumors ($n = 25$). For the remaining patients, the risk estimates for extraprostatic growth ranged from 7.5% to 48.1% (median 31.1%).

The MSKCC nomogram, Partin tables, and mpMRI results were all significant predictors of locally advanced disease in univariable analysis, see Table 3. In multivariable analysis, mpMRI remained a significant predictor in addition to both the MSKCC nomogram and Partin tables, see Table 4.

ROC curves for mpMRI, MSKCC, and Partin tables, as well as the combinations MSKCC + mpMRI and Partin + mpMRI are displayed in Figs. 1 and 2. The AUC of the mpMRI results (AUC 0.61) was similar to the AUC of the Partin tables (0.62), but lower than the AUC of the MSKCC nomogram (0.73; outside the 95% CI). Combining the nomograms with mpMRI results increased diagnostic accuracy marginally (AUC MSKCC + mpMRI 0.74; AUC Partin + mpMRI 0.66).

4. Discussion

Accurate staging of the local tumor in primary prostate care remains a challenging diagnostic matter. The recent AUA statement on mpMRI for CaP notes that there is “currently insufficient evidence to recommend MRI for screening, staging.” Yet, it also states that “MRI before selecting definitive therapy can be beneficial for men with a presumed clinically localized prostatic adenocarcinoma” [16]. In our previous report, we found unsatisfactory accuracy of mpMRI for local staging as stand-alone diagnostic modality [13]. Here, we provide an analysis of the added value of mpMRI when combined with clinical prediction models, that is, staging nomograms.

Table 2
Characteristics of 430 patients who underwent a robot assisted radical prostatectomy and preoperative multiparametric MRI. Median and interquartile ranges

Patient characteristics and pathology results		
Age (years)	66 (61−69)	
PSA (ng/ml)	9.2 (6.2−14.9)	
prostate volume (ml)	48 (37−65)	
number of biopsy cores	8 (8−10)	
% of positive biopsy cores	49.1	
Gleason score	*Biopsy results, n (%)*	*RARP results, n (%)*
6	156 (36)	88 (21)
7	182 (42)	266 (62)
8	59 (14)	38 (9)
9	27 (6)	32 (8)
10	5 (1)	2 (0)
Tumor-stage	*Radiologic T-stage, n (%)*	*RARP T-stage, n (%)*
T0	70 (16)	4 (1)
T2	227 (53)	289 (67)
T3a	117 (27)	76 (18)
T3b	15 (3)	57 (13)
T4	1 (0)	4 (1)

Table 3
Univariable analysis of the MSKCC nomogram score, Partin table score, and mpMRI results (radiologic T3-4) predicting locally advanced disease (pathologic T3-4)

Parameter	Odds ratio	95% CI		Sign.
MSKCC score *(per %)*	1.06	1.05	1.08	<0.01
Partin score *(per %)*	1.04	1.02	1.06	<0.01
Radiologic T3-4	2.58	1.68	3.97	<0.01

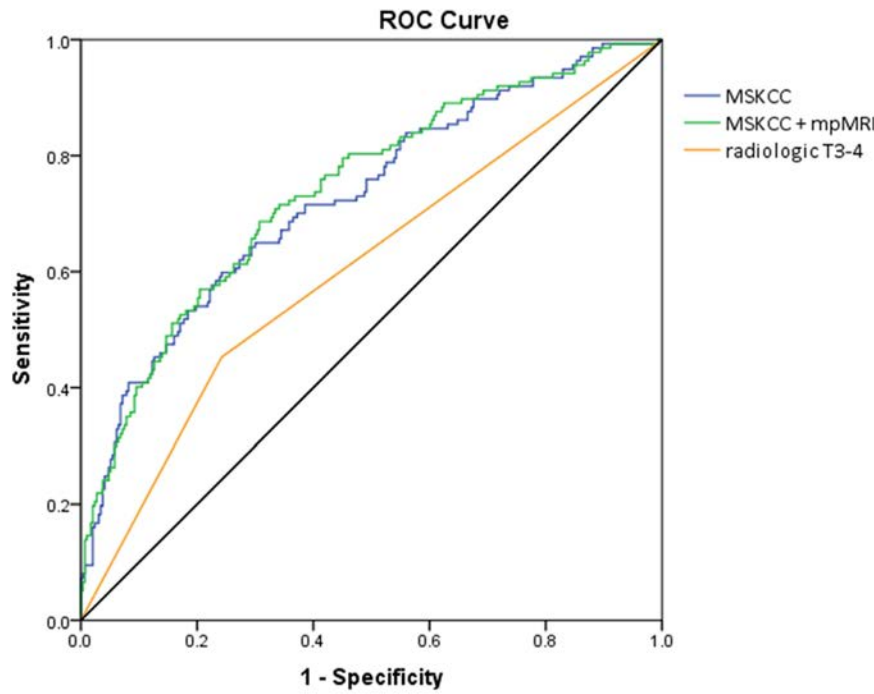
Table 4
Multivariable analysis of the MSKCC nomogram and mpMRI results (radiologic T3-4) and the Partin Table and mpMRI results, predicting locally advanced disease (pathologic T3-4)

Parameter	Odds ratio	95% CI		Sign.
MSKCC score *(per %)*	1.06	1.04	1.08	<0.01
Radiologic T3-4	1.9	1.20	3.04	0.01
Partin score *(per %)*	1.04	1.01	1.06	<0.01
Radiologic T3-4	2.13	1.34	3.40	<0.01

In our cohort of 430 RARP patients, the observed AUCs of the MSKCC (0.73) and Partin (0.62) nomograms for the prediction of nonorgan confined disease are in line with previously reported AUCs for these models [14,17−21] and indicate *fair* (MSKCC) to *limited* (Partin) diagnostic accuracy. mpMRI appeared to provide a significant addition to the nomograms in multivariable analysis, yet the AUC of the combined models increased with only 1% (MSKCC + mpMRI) and 4% (Partin + mpMRI) (absolute percentages). Balancing the limited added diagnostic accuracy against the costs and patient discomfort related to performing mpMRI, it remains doubtful whether mpMRI should be included in the standard diagnostic work-up prior to radical treatment in current clinical practice.

In the few previous studies that combined mpMRI with staging nomograms, the tumor substages were investigated separately (e.g., separating T3a from T3b) [18−20]. However, as described in the EAU guidelines, substaging is secondary to the distinction between locally advanced (T3-4) and organ-confined disease (T0-2), for this distinction influences treatment [2]. In the present study, the dichotomization in locally advanced vs. organ-confined disease was followed, to evaluate the true clinical value of mpMRI.

Our results are in line with the recent report by Weaver et al. [19], which found limited additional value of mpMRI over the MSKCC nomogram. There are some methodological differences, however. First, the sample size of our study



predictor	AUC	95% CI		sign.
MSKCC	0.73	0.67	0.78	<0.01
MSKCC+mpMRI	0.74	0.69	0.79	<0.01
Radiologic T3-4	0.61	0.55	0.66	<0.01

Fig. 1. Receiver operating charecteristics (ROC) curves and Area Under the Curve (AUC) for the MSKCC nomogram, the combined MSKCC + mpMRI model and the mpMRI results (radiologic T3-4), predicting locally advanced disease (pathologic T3-4).

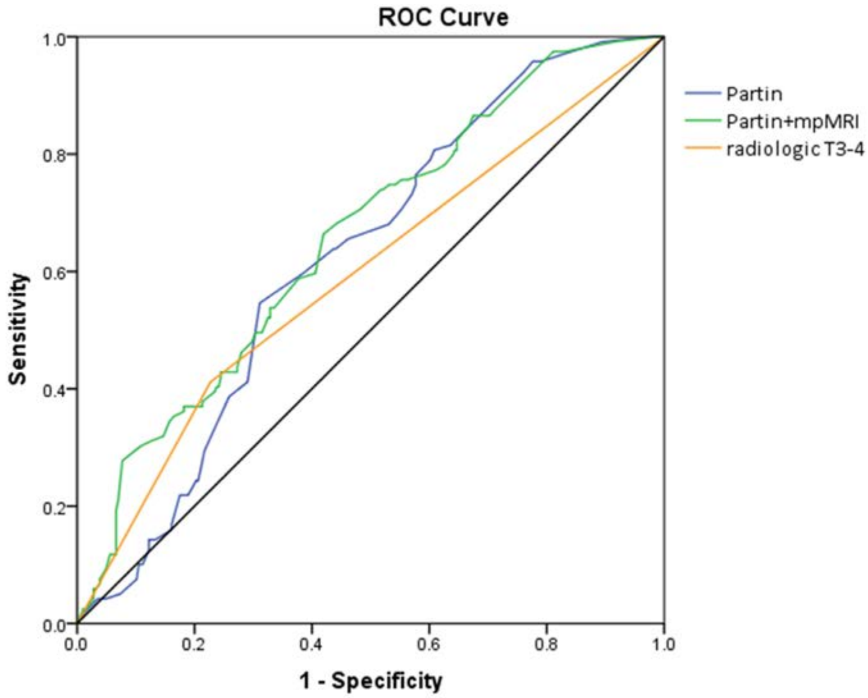
is considerably larger ($n = 430$ vs $n = 237$, respectively). Second, extracapsular extension was noted in only 16% of men undergoing mpMRI in the study by Weaver et al., which is little compared to our series (31%) [13] and that of others (29%; 29.3%) [18,20]. This might have hampered the study of Weaver et al. to accurately assess the diagnostic value of mpMRI. Lastly, Weaver et al. classified mpMRI outcomes as positive when either extracapsular extension *or* a PI-RADS 5 lesion was detected. However, the PI-RADS scores are not intended as a staging parameter. Furthermore, it may overlap with variables already included in the nomogram (e.g., the biopsy Gleason score, the number of positive biopsy cores) [22,23]. As such, we choose to solely regard radiologic T-stage in this study (in accordance with other previous studies).

In the extensive report by Morlacco et al. [20] the AUC for the prediction of extraprostatic growth increased from 0.61 to 0.73 when mpMRI results were added to the Partin tables. Clearly, this was a high-risk group of patients, with 39% having a Gleason score ≥8 and 49% pT3-4 on final pathology. The authors note that the accuracy of mpMRI for the detection of locally advanced disease stages is better in intermediate to high-risk patients [21], possibly increasing the added value of mpMRI for staging in their study.

Feng et al. [18] provide the only previous analysis of mpMRI in combination with both the MSKCC nomogram and the Partin tables ($n = 112$). The reported AUCs of the MSKCC and Partin models were 0.86 and 0.85 respectively, rising to 0.92 and 0.94 when combined with mpMRI results. Although statistically significant, discussion remains whether the observed added value by Feng et al. truly justifies the use MRI and its related costs and patients' discomfort—especially considering the outstanding accuracy of mpMRI in this study (sensitivity 85.4%), which is not universally achieved.

Our study has several limitations. The staging accuracy (sensitivity 45.3%) of our mpMRI procedures appears on the lower side of earlier published studies [12]. Radiologic (in)experience or the absence of reevaluation by specialized radiologists potentially contributed to lower diagnostic accuracy, although this remains topic of discussion [12,13]. Tay et al. [24] compared the added value of *specialist-reviewed* vs. *nonspecialist reviewed* mpMRI to existing clinical parameters (not to predefined nomograms). They showed that nonspecialist reviewed mpMRI added little diagnostic certainty to the clinical parameters (AUC rising from 0.69 to 0.72), whereas specialists-reviewed mpMRI did improve diagnostic accuracy (AUC rising to 0.90).

It remains to be answered whether more specialization of radiologists allows for meaningful *added* diagnostic value of mpMRI to preoperative nomograms. Indeed, it might be



predictor	AUC	95% CI		sign.
Partin	0.62	0.57	0.68	<0.01
Partin+mpMRI	0.66	0.60	0.71	<0.01
Radiologic T3-4	0.59^{e}	0.53	0.65	0.03

Fig. 2. Receiver operating curves (ROC) curves and Area Under the Curve (AUC) for the Partin tables, the combined Partin + mpMRI model and the mpMRI results (radiologic T3-4), predicting locally advanced disease (pathologic T3-4).

argued that the slight increase in accuracy attained with nonspecialized radiologists in this study should prompt further investigation with specialized interpreters. However, in the cited study by Feng et al., all mpMRI scans were reviewed by a single highly specialized radiologist and the added value remained limited (discussed above). The value of our report lies in the fair representation of daily clinical practice and current radiologic experience in contemporary urologic reference centers. In this scenario, mpMRI offers limited additional value over the staging nomograms.

The inclusion criteria for this study were a preoperative mpMRI, as well a radical prostatectomy. Inherently, this includes some selection bias. It is possible that in the case of clear radiologic evidence for locally advanced disease, some urologists might have had a preference to opt for radiation therapy instead of surgery. This would lead to poorer mpMRI outcomes in our radical prostatectomy group, as only the patients with less clear radiologic results might have been included. However, the evaluation of mpMRI accuracy in RARP patients remains the only way to compare the imaging technique to pathology results (i.e., the golden standard). Moreover, the accuracy of mpMRI is especially relevant in patients prior to scheduled surgery, as (radiologic) staging influences decisions on nerve-sparing techniques in this group.

5. Conclusion

In this study, mpMRI results were combined with the preoperative MSKCC and Partin nomograms to predict the presence of locally advanced prostate cancer. We found that the addition of mpMRI does not improve prediction of pathologic stage compared to the nomograms alone.

Conflict of Interest

The authors declare no conflicts of interest to this manuscript, financial or otherwise.

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