# Multiparametric magnetic resonance imaging and frozen-section analysis efficiently predict upgrading, upstaging, and extraprostatic extension in patients undergoing nerve-sparing robotic-assisted radical prostatectomy

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## Abstract

To evaluate the role of multiparametric magnetic resonance imaging (mpMRI) in predicting upgrading, upstaging, and extraprostatic extension in patients with low-risk prostate cancer (PCa). MpMRI may reduce positive surgical margins (PSM) and improve nerve-sparing during robotic-assisted radical prostatectomy (RARP) for localized prostate cancer PCa.

This was a retrospective, monocentric, observational study. We retrieved the records of patients undergoing RARP from January 2012 to December 2013 at our Institution. Inclusion criteria were: PSA <10 ng/mL; clinical stage <T3a; biopsy Gleason score <7; prostate mpMRI performed preoperatively at our Institution; intraoperative FSA of the posterolateral aspects of the specimen.

All the identified lesions were scored according to the Prostate Imaging Reporting and Data System (PIRADS). We considered the lesion with the highest PIRADS score as index lesion. All the included patients underwent nerve-sparing RARP. During surgery, the specimen was sent for FSA of the posterolateral aspects. The surgeon, according to the localization scheme provided by the mpMRI, inked the region of the posterolateral aspect of the prostate that had to be submitted to FSA.

We evaluated association between clinical features and PSM, upgrading, upstaging, and presence of unfavorable disease.

Two hundred fifty-four patients who underwent nerve-sparing RARP were included. PSM rate was 29.13% and 15.75% at FSA and final pathology respectively. Interestingly, the use of FSA reduced PSM rate in pT3 disease (25.81%). Higher PIRADS scores demonstrated to be related to high probability of upgrading and upstaging. This significativity remains even when considering PIRADS 2–3 versus 4 versus 5 and PIRADS 2–3 versus 4–5. Also PSM at FSA were associated with higher probability of upgrading and upstaging.

PIRADS score and FSA resulted to be strictly related to grading and staging, thus being able to predict upgrading and/or upstaging at final pathology.

**Abbreviations:** AUC = area under curve, BCR = biochemical recurrence, BPH = benign prostatic hyperplasia, CI = confidence interval, CSM = cancer-specific mortality, DCE = dynamic contrast-enhanced, DWI = diffusion-weighted, EPE = extraprostatic extension, ESUR = European Society of Urogenital Radiology, FSA = frozen-section analysis, GS = Gleason score, mpMRI = multiparametric magnetic resonance imaging, NVB = neurovascular bundle, OR = odds ratio, PCa = prostate cancer, PIRADS = Prostate Imaging Reporting and Data System, PSA = prostatic-specific antigen, PSM = positive surgical margins, RARP = robotic-assisted radical prostatectomy, ROC = receiver operating characteristics, ROI = region of interest, T2w = T2-weighted.

**Keywords:** low-risk, magnetic resonance imaging, prostate cancer, surveillance, upgrading, upstaging

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## 1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) and frozen-section analysis (FSA) may play an important role in reducing positive surgical margins (PSM) during nerve-sparing robotic-assisted radical prostatectomy (RARP) for localized prostate cancer (PCa). Anyway, only a few evidences supporting the combined use of these 2 instruments are available.[1]

Recently, mpMRI has been applied not only to identification of lymph nodes involvement but also to the identification of high-risk cancer areas within the prostate, which are sometimes missed by standard prostate biopsy.[2]

Moreover, mpMRI proved to be reliable in identifying extraprostatic extension (EPE) or seminal vesicles involvement,[3] and in detecting anterior zone PCa, which is often missed by prostate biopsy.[4]

Thus, mpMRI is becoming a very useful planning tool in the clinical pathway for localized PCa, gaining a role in the risk stratification.

MpMRI includes high-resolution T2-weighted sequences (T2w), diffusion-weighted sequences (DWI), dynamic contrast-enhanced images (DCE), and spectroscopy.

T2w sequences have high spatial resolution ($0.6 \times 0.7$ mm pixels), and can define the relationships between the suspect lesion and the prostatic capsule, reaching a sensitivity of 48% to 88% and a specificity of 44% to 81%.[5,6]

DWI sequences, which measure the diffusion of water molecules within the tissues (reduced in cancerous tissue), associated with high-resolution T2w sequences, enhance sensitivity and specificity to 85% to 90%.[7]

DCE sequences provide with a perfusional map of the region of interest (ROI) identified by the previous sequences. In high-grade malignant lesions, early enhancement and early washout are present, while in benign prostatic hyperplasia (BPH) areas washout is slow.[8] Adding these sequences brings sensitivity and specificity to 90% to 95%.[9]

Spectroscopy is a technique that indirectly measures the concentration of some metabolites within the ROI. Particularly, intracellular concentrations of choline, creatine (which increase in cancerous lesions), and citrate (which decrease with growing cancer grade and volume) are estimated. Spectroscopy brings specificity to 98%, but, on the other hand, sensitivity is only 53%.

Correct interpretation of mpMRI may be challenging, so the European Society of Urogenital Radiology (ESUR) produced a standardized score to describe prostatic lesions. This system, similarly to the existing Breast Imaging Reporting and Data System, has been called Prostate Imaging Reporting and Data System (PIRADS).[10]

The aim of the PIRADS is to uniform interpretation of mpMRI images to predict the clinical relevance of the identified lesions. This probability is expressed by means of a score ranging from 1 (very unlikely) to 5 (very likely).

The validity of the PIRADS has been confirmed by Kuru et al,[11] who compared PIRADS score assigned to prostatic lesions with biopsy Gleason score (GS).

FSA can be implied to identify EPE and so to decide whether or not to spare the neurovascular bundle (NVB):[12] this way, PSM rates can be reduced.

FSA of macroscopically suspicious prostatic tissue fragments resulted to have low sensitivity.[13] Sensitivity improves when all the posterolateral aspects of the prostate, which are in contact with the NVB, are examined.[12]

Even if PSM alone are not associated with an increase of cancer-specific mortality (CSM) in the 15 years following radical prostatectomy, reducing PSM results in less biochemical recurrences (BCR), secondary therapies, and patient anxiety.[14]

The aim of this study was to evaluate the role of prostate mpMRI as a predictor of upgrading, upstaging, and EPE and the use of FSA as a predictor of PSM.

## 2. Materials and methods

This was a retrospective, monocentric, observational study. We retrieved the records of patients undergoing nerve-sparing RARP from January 2012 to December 2013 at our Institution. Inclusion criteria were: initial prostatic-specific antigen (PSA) <10 ng/mL; clinical stage <T3a; biopsy GS <7; prostate mpMRI performed preoperatively at our Institution; intraoperative FSA

of the posterolateral aspects of the specimen. The Institutional Review Board approved the study.

Patients with history of previous prostatic surgery (e.g., for BPH), preoperative hormone therapy, previous external beam radiotherapy, or brachytherapy were excluded. All the identified lesions were scored according to PIRADS. We considered the lesion with the highest PIRADS score as index lesion. Two experienced radiologists (GP and SA) evaluated all the mpMRIs, reporting their conclusions on a standard reporting scheme, a useful tool for the surgeon to localize the lesions (Fig. 1).

All mpMRIs were performed with a 1.5 Tesla device. T2w, DWI, and DCE sequences were obtained.

All the included patients underwent nerve-sparing RARP. During surgery, after the removal of the prostate, the specimen was sent for FSA of the posterolateral aspects. The surgeon, according to the localization scheme provided by the mpMRI, inked the region of the posterolateral aspect of the prostate that had to be submitted to FSA.

Experienced uropathologists prepared the specimen for FSA; 5 μm sections were analyzed at optical microscopy. FSA results were reported to the surgeon: margins were defined as negative, focally positive ($\leq$1 mm), positive (>1 mm), or with cancer present at <1 mm from the inked margin.

In case of extensively positive margin, total NVB removal was performed; in case of focally positive margin, only partial resection of the NVB was performed.

### 2.1. Statistical analysis

PSM were defined as the presence of cancer on the surgical margin during FSA or at final pathology. The disease was defined "unfavorable" when final pathology reported at least an upgrading (GS$\geq$7) or an upstaging$\geq$pT3a. Association between clinical features and PSM, upgrading, upstaging, and presence of unfavorable disease has been evaluated with the $\chi^2$ test or Fisher test for categorical variables. Non-parametric Wilcoxon test has been applied to independent samples, while the $T$ test has been used for continuous variables.

By means of non-conditioned logistic regression models, we calculated the odds ratios (ORs) with their confidence intervals (CIs) for PSM, upgrading, upstaging, and unfavorable disease.

With each model, we evaluated PIRADS 2–3 versus PIRADS 4 versus PIRADS 5 lesions, and PIRADS 2–3 versus PIRADS 4–5 lesions.

Finally, we compared each model including or not including PIRADS score, and designed the receiver operating characteristics (ROC) curves to find out if the difference between the areas under curve (AUC) was significant according to the De Long test.[15]

For all analyses, a $P$ value <0.05 was used to indicate statistically significance.

Statistically analysis was performed with SAS software ver. 9.2.

## 3. Results

Two hundred fifty-four patients who underwent nerve-sparing RARP were included. Mean age was $62.6 \pm 7.17$ years. Mean pretreatment PSA was $6.1 \pm 1.95$ ng/mL.

Two hundred two (79.53%) patients had T1 disease (1 T1a and 202 T1c). Fifty-two (20.47%) patients had cT2 disease (49 with cT2a and 3 with cT2b disease).

Preoperative mpMRI showed at least 1 PIRADS 5 lesion in 96 patients (37.8%), at least 1 PIRADS 4 in 102 (40.16%), 1
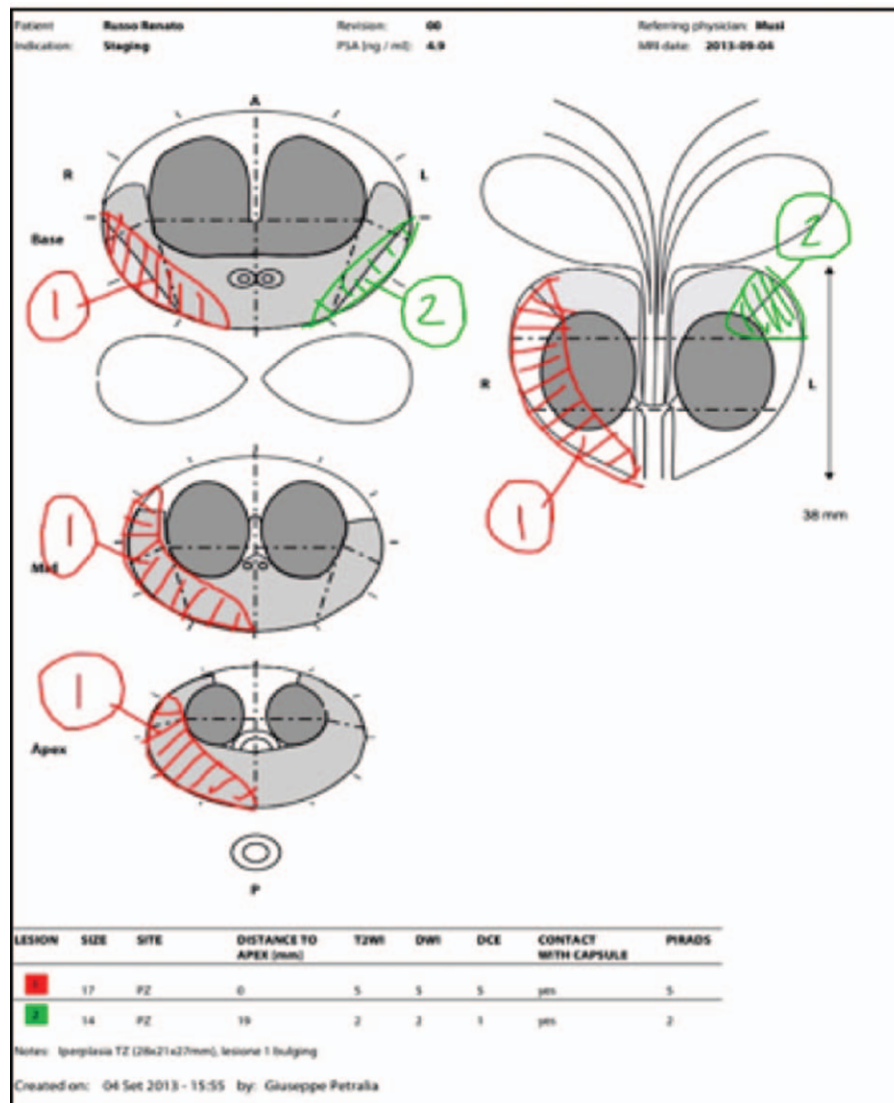
**Figure 1.** Standard reporting scheme for lesions identified by mpMRI. mpMRI = multiparametric magnetic resonance imaging.

PIRADS 3 in 45 (17.72%), and only a PIRADS 2 lesion in 11 (4.33%).

During surgery, 191 (75.20%) patients had bilateral nerve-sparing, 47 (18.50%) monolateral nerve-sparing, while, in 16 (6.30%) patients, nerve-sparing was not feasible.

Median time to receive FSA results was 35 minutes.

At final pathology, staging was pT2a in 23 (9.05%) patients, pT2b in 5 (1.97%), pT2c in 164 (64.57%), pT3a in 56 (22.05%), and pT3b in 6 (2.46%). One patient (0.39%) had GS 5, 124 patients (48.82%) had GS 6, 125 (49.21%) GS 7, 3 (1.18%) GS 8, and 1 (0.39%) GS 9.

The features of the included population are shown in Table 1.

First, we analyzed PSM rates. 74 patients (29.13%) had PSM at FSA, while 40 (15.75%) had PSM at final pathology (P < 0.05). Of these 74 patients, 44 (59.46%) had T2 disease, while 30 (40.54%) had T3 (Table 2).

We then analyzed PSM rates according to pathological stage. Of 192 patients with pT2 disease, 44 (22.92%) had PSM at FSA and 24 (12.50%) had PSM at final pathology. Of the 44 patients with PSM at FSA, 38 had negative margins at final pathology

after radicalization. Of 148 with pT2 disease and negative margins at FSA, 18 had PSM at final pathology (Table 3).

Of 62 patients with pT3 disease, 30 (48.39%) had PSM at FSA; of them, 21 had negative margins at final pathology after radicalization. Of the 31 pT3 patients with negative margins at FSA, 7 had PSM at final pathology (Table 4).

Of 198 patients with PIRADS 4 or 5 lesions, 64 (32.32%) had PSM at FSA; of them, 28 resulted to be pT3 and 36 pT2. Thirty-two patients (16.16%) had PSM at final pathology (15 pT3 and 17 pT2) (Table 5).

One hundred eighty patients had negative margins at FSA; of them, 25 (13.89%) had PSM at final pathology.

We investigated the association between the preoperative clinical features of patients who had PSM at FSA or at final pathology and PIRADS score at mpMRI.

Interestingly, age resulted to be statistically significant. Patients aged 63.5 ± 7.8 are more likely to have PSM than patients aged 61.9 ± 6.7 (P = 0.02).

Higher PIRADS scores resulted to be related to the probability of PSM (Table 6). Statistical significance was present at univariate

## Table 1

**Features of the included population.**

|  | N (%) |
|---|---|
| Age* | 62.6 (±7.17) |
| Clinical stage |  |
| cT1a-1c | 202 (79.53%) |
| cT2a-2c | 52 (20.47%) |
| PSA* | 6.1 (±1.95) |
| Pathological stage |  |
| pT2a | 23 (9.05%) |
| pT2b | 5 (1.97%) |
| pT2c | 164 (64.57%) |
| pT3a | 56 (22.05%) |
| pT3b | 6 (2.46%) |
| Gleason Score sum |  |
| 5 | 1 (0.39%) |
| 6 | 124 (48.82%) |
| 7 | 125 (49.21%) |
| 8 | 3 (1.18%) |
| 9 | 1 (0.39%) |
| PIRADS |  |
| 2 | 11 (4.33%) |
| 3 | 45 (17.72%) |
| 4 | 102 (40.16%) |
| 5 | 96 (37.80%) |

PIRADS = Prostate Imaging Reporting and Data System, PSA = prostatic-specific antigen.
* = (±SD).

($P=0.01$), but not at multivariate analysis, as shown by the ROC curves (Fig. 2A and B).

Considering the association between the preoperative features of patients with pT3 disease, PIRADS score, and FSA, all univariate analyses demonstrated statistical significance.

Patients with cT2 disease resulted to have a 3-fold probability (OR 3.2) to have pT3 disease when compared with patients with T1c disease ($P=0.002$ at multivariate analysis).

From this analysis, we showed that patients with PIRADS 5 lesions at mpMRI had higher probability to present with pT3 disease (OR 3.41; $P=0.001$ at multivariate analysis). Similarly, patients with PSM at FSA had higher probability to have pT3 disease (OR 2.59; $P=0.004$).

When grouping mpMRI-evidenced lesions in PIRADS 2–3 and 4–5, statistical significance is lost, since patients with PIRADS 4 lesion had higher probability to have T3 disease (OR 1.17), but not in statistically significant way ($P=0.21$) (Table 7 and Fig. 3).

We also analyzed the association between features of patients with GS≥7 and PIRADS score. PIRADS score was related to the probability of a GS upgrade to≥7 at final pathology both at univariate ($P=0.0003$) and multivariate analyses ($P=0.02$). In

## Table 2

**PSM at FSA and final pathology according to pathological staging.**

|  | pT2 (% PSM) | pT3 (% PSM) | Total (% PSM) |
|---|---|---|---|
| Margins at FSA |  |  |  |
| Negative | 148 | 32 | 180 (70.87) |
| Positive | 44 (22.92) | 30 (48.39) | 74 (29.13) |
| Margins at final pathology |  |  |  |
| Negative | 168 | 46 | 214 (84.25) |
| Positive | 24 (12.5) | 16 (25.81) | 40 (15.75) |

FSA = frozen-section analysis, PSM = positive surgical margins.

## Table 3

**Surgical margins in patients with pT2 disease.**

| pT2 | FSA |  | Final pathology | |
|---|---|---|---|---|
|  |  |  | Positive | Negative |
|  | Positive | 44 (22.92%) | 6 | 38 |
| 192 | Negative | 148 | 18 | 130 |
|  | Total | 192 | 24 (12.5%) | 168 |

FSA = frozen-section analysis.

fact, patients with at least 1 PIRADS 4 lesion had almost twice the probability to have GS≥7, while patients with PIRADS 5 had more than 3 times the probability to have GS≥7 when compared with patients with PIRADS 2 to 3 lesions.

Similarly significant is the association between GS at final pathology and FSA. In fact, patients with PSM at FSA had almost 3 times the probability to have a GS upgrade to≥7 (OR 2.7; $P=0.001$). Significance is also present when grouping patients with PIRADS 4–5 versus PIRADS 2–3 (Table 8, Fig. 4).

Finally, we evaluated upgrading and upstaging at final pathology in correlation with the preoperative features of the included patients.

Higher PIRADS scores demonstrated to be related to high probability of upgrading and upstaging (OR 4.72 for PIRADS 5); both at univariate and multivariate analyses, $P$ value was <0.05. This significativity remains even when considering PIRADS 2–3 versus 4 versus 5 and PIRADS 2–3 versus 4–5.

Also PSM at FSA were associated with higher probability of upgrading and upstaging ($P<0.05$ at univariate analysis) (Table 9 and Fig. 5).

## 4. Discussion

In our study, PSM rate was 29.13% and 15.75% at FSA and final pathology respectively. Interestingly, the use of FSA reduced PSM rate in pT3 disease, which resulted 25.81%, lower than what is reported in the literature.[16]

We did not distinguish between focally and extensively positive surgical margins. Our incidence of PSM at FSA can also be explained by our attempt to perform intrafascial nerve-sparing, which is more prone to PSM but demonstrated significantly better sexual function outcomes.[17]

In the present series, RARP were performed by 8 different surgeons, of which 3 were "high-volume" surgeons (> 50 cases per year), while 5 performed less than 50 cases per year. The use of FSA, guided by mpMRI, allowed reducing PSM despite this fact.

PSM, defined as the presence tumor at the inked margin of the prostatectomy specimen, are a risk factor for disease progression after surgery.[18] The impact of PSM on cancer-related outcome has been studied extensively, even if a clear association between

## Table 4

**Surgical margins in patients with pT3 disease.**

| pT3 | FSA |  | Final pathology | |
|---|---|---|---|---|
|  |  |  | Positive | Negative |
| 62 | Positive | 30 (48.39%) | 9 | 21 |
|  | Negative | 32 | 7 | 25 |
|  | Total | 62 | 16 (25.81%) | 46 |

FSA = frozen-section analysis.

**Table 5**

Margins and pathological stage in patients with PIRADS 4 or 5 lesions.

| PIRADS 4 or 5 | | Margins at FSA | | Margins at final pathology | |
|---|---|---|---|---|---|
| | | Positive | Negative | Positive | Negative |
| pT3 | 55 | 28 | 27 | 15 | 40 |
| pT2 | 143 | 36 | 107 | 17 | 126 |
| Total | 198 | 64 | 134 | 32 | 166 |

FSA = frozen-section analysis, PIRADS = Prostate Imaging Reporting and Data System.

PSM and CSM was shown in only a single large population-based study, indicating that patients with PSM had a 1.7-fold higher risk of death compared with those without.[19]

The mean PSM rate reported in large systematic review was 9% in pT2 diseases, 37% in pT3, and 50% in pT4,[16] which is consistent with the data we obtained from our study.

Sooriakumaran et al[20] showed how surgical experience heavily influences the incidence of PSM.

The use of FSA to reduce PSM has been previously reported. In 2002, Goharderakhshan et al[21] reported the experience of 101 patients undergoing open mono- or bilateral nerve-sparing radical prostatectomy: FSA has been performed on the prostatectomy specimens, which was consistent with final pathology in 91% of cases. Positive and negative predictive value of FSA resulted to be 73% and 94% respectively.

More recently, Schlomm et al reported the outcomes on 5392 patients who underwent FSA of the whole margin near to the NVB during nerve-sparing radical prostatectomy. PSM occurred in 25% of cases. After radicalization of the involved NVB, 86% had negative margins at final pathology.[22] Similar results have been reported by Von Bodman et al.[23]

In the present study, significant association emerged between PIRADS 4–5 and PSM at FSA, upgrading and upstaging.

Higher PIRADS scores resulted to be related to higher probability of pT3 disease; particularly, this probability was statistically significant for PIRADS 5. In fact, mpMRI with T2-weighted sequences, DCE, and spectroscopy reaches almost 80% accuracy in diagnosing EPE.[24]

In our series, rather than with biopsy GS as reported by Kuru et al[11] PIRADS seem to have a good correlation with GS on the surgical specimen.

MpMRI excludes the presence of a clinically relevant prostate cancer with a specificity and negative predictive value of 90% to 95%. Thus, potential applications of mpMRI to prostate cancer diagnosis can be: improve prostate biopsy sensitivity in patients with intermediate- and high-risk prostate cancer; reduce low-risk disease overdiagnosis; avoid biopsy in younger patients with nonsuspicious mpMRI; exclude high-risk disease in patients with elevated PSA and negative prostate biopsies.[25]

MpMRI is particularly useful to identify high-grade and significant-volume cancers. T2-weighted sequences precisely identify disease foci when GS is $\geq 7$ and volume is $\geq 0.5$ cm³.[26] DW sequences and spectroscopy are related to GS too. Villeirs et al[27] confirmed how mpMRI can identify a GS $\geq 7$ lesion with a 93% sensitivity and a 93% specificity, which is really impressive when compared with a 68% sensitivity for GS 6 disease.

Marcus et al studied the influence of mpMRI on risk stratification of prostate cancer. On 71 total patients, 12 (16.9%) have reclassified to a higher risk class due to mpMRI findings, while in 6 patients (8.5%) mpMRI changed the therapeutic strategy. MpMRI specificity for pT3 disease resulted to be 92.9%.[28]

**Table 6**

Association between the clinical features of the patients and PSM*: univariate and multivariate analysis with PIRADS 2–3 versus PIRADS 4 versus PIRADS 5, and PIRADS 2–3 versus PIRADS 4–5.

| | PSM* | | | | |
|---|---|---|---|---|---|
| | Yes N (%) | No N (%) | P value‡ | Multivariate odds ratio (95% CI) | P value |
| Age† | 63.5 (±7.8) | 61.9 (±6.7) | **0.02** | 1.02 (0.98–1.06) | 0.27 |
| Clinical stage | | | 0.19 | | 0.17 |
| cT1a-1c | 73 (74%) | 129 (83%) | | 1.00 (reference) | |
| cT2a-2c | 26 (26%) | 26 (17%) | | 1.56 (0.83–2.95) | |
| PSA† | 6.2 (±1.9) | 5.9 (±2.0) | 0.25 | 1.07 (0.94–1.22) | 0.33 |
| PIRADS | | | **0.01** | | |
| 2 | 0 (0%) | 11 (7%) | | 1.00 (reference) | |
| 3 | 16 (16%) | 29 (19%) | | | |
| 4 | 38 (38%) | 64 (41%) | | 1.42 (0.69–2.89) | 0.93 |
| 5 | 45 (46%) | 51 (33%) | | 1.92 (0.93–3.94) | 0.09 |
| Age† | 63.5 (±7.8) | 61.9 (±6.7) | **0.02** | 1.02 (0.99–1.06) | 0.22 |
| Clinical stage | | | 0.19 | | 0.15 |
| cT1a-1c | 73 (74%) | 129 (83%) | | 1.00 (reference) | |
| cT2a-2c | 26 (26%) | 26 (17%) | | 1.60 (0.85–3.01) | |
| PSA† | 6.2 (±1.9) | 5.9 (±2.0) | 0.25 | 1.08 (0.94–1.23) | 0.29 |
| PIRADS | | | 0.07 | | 0.14 |
| 2–3 | 16 (16%) | 40 (26%) | | 1.00 (reference) | |
| 4–5 | 83 (84%) | 115 (74%) | | 1.64 (0.85–3.15) | |

Significative ORs and P values are in bold.

FSA = frozen-section analysis, PIRADS = Prostate Imaging Reporting and Data System, PSA = prostatic-specific antigen, PSM = positive surgical margins.

* PSM at FSA or final pathology.

† ±SD.

‡ T test for continuous variables; $\chi^2$ test or Fisher exact test for categorical variables.
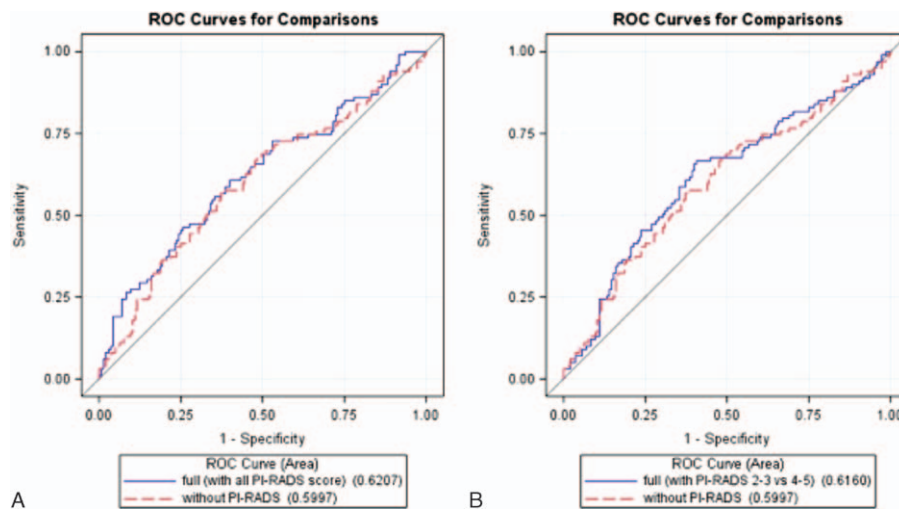
**Figure 2.** Comparison between ROC curves for PSM at FSA or final pathology. A, All PIRADS score (*P*=0.39). B, PIRADS 2–3 versus PIRADS 4–5 (*P*=0.39). FSA = frozen-section analysis, PIRADS = Prostate Imaging Reporting and Data System, PSM = positive surgical margins, ROC = receiver operating characteristics.

MpMRI has also been suggested to improve functional outcomes in patients undergoing nerve-sparing RARP. McClure et al demonstrated that mpMRI could change surgical strategy in nerve-sparing RARP. In 28 of 104 included patients, mpMRI provided the surgeon with data that changed the decision of performing a nerve-sparing procedure: interestingly, 17 patients,

not intended to receive a nerve-sparing, had it after mpMRI suggested its feasibility: no PSM occurred in these patients.[29] Also, Hricak et al[30] evidenced that MRI may support the surgeon in deciding to perform a nerve-sparing procedure.

Our results are consistent with the available results. PIRADS 5 lesions are associated with EPE and PSM at FSA or final

## Table 7

**Association between clinical features and pT3 disease: univariate and multivariate analyses; PIRADS 2–3 versus PIRADS 4 versus PIRADS 5; PIRADS 2–3 versus PIRADS 4–5.**

| | pT3 | | | | |
|---|---|---|---|---|---|
| | Yes N (%) | No N (%) | P value[†] | Multivariate odds ratio (95% CI) | P value |
| Age* | 63.0 (±8.7) | 62.4 (±6.6) | 0.28 | 0.98 (0.94–1.03) | 0.41 |
| Clinical stage | | | **0.001** | | **0.002** |
| cT1a-1c | 39 (63%) | 163 (85%) | | 1.00 (reference) | |
| cT2a-2c | 23 (37%) | 29 (15%) | | **3.20 (1.56–6.59)** | |
| PSA* | 6.4 (±2.2) | 5.9 (±1.8) | 0.18 | 1.15 (0.97–1.36) | 0.11 |
| PIRADS | | | **0.0003[‡]** | | |
| 2 | 1 (2%) | 10 (5%) | | 1.00 (reference) | |
| 3 | 6 (10%) | 39 (21%) | | | |
| 4 | 17 (27%) | 85 (44%) | | 1.17 (0.44–3.12) | 0.21 |
| 5 | 38 (61%) | 58 (30%) | | **3.41 (1.33–8.72)** | **0.001** |
| Margins at FSA | | | **0.0001** | | **0.004** |
| Negative | 32 (52%) | 148 (77%) | | 1.00 (reference) | |
| Positive | 30 (48%) | 44 (23%) | | **2.59 (1.35–4.94)** | |
| Age* | 63.0 (±8.7) | 62.4 (±6.6) | 0.28 | 0.99 (0.95–1.03) | 0.64 |
| Clinical stage | | | **0.001** | | **0.001** |
| cT1a-1c | 39 (63%) | 163 (85%) | | 1.00 (reference) | |
| cT2a-2c | 23 (37%) | 29 (15%) | | **3.28 (1.62–6.60)** | |
| PSA* | 6.4 (±2.2) | 5.9 (±1.8) | 0.18 | 1.16 (0.99–1.37) | 0.07 |
| PIRADS | | | **0.02[§]** | | 0.11 |
| 2–3 | 7 (11%) | 49 (26%) | | 1.00 (reference) | |
| 4–5 | 55 (89%) | 143 (74%) | | 2.05 (0.84–4.98) | |
| Margins at FSA | | | **0.0001** | | **0.001** |
| Negative | 32 (52%) | 148 (77%) | | 1.00 (reference) | |
| Positive | 30 (48%) | 44 (23%) | | **2.80 (1.49–5.25)** | |

Significant ORs and P values are in bold.

* = (± SD).

[†] T test for continuous variables; $\chi^2$ test or Fisher exact test for categorical variables.

[‡] Mantel–Haenszel P value for trend: <0.0001.

[§] Mantel–Haenszel P value for trend: 0.02.
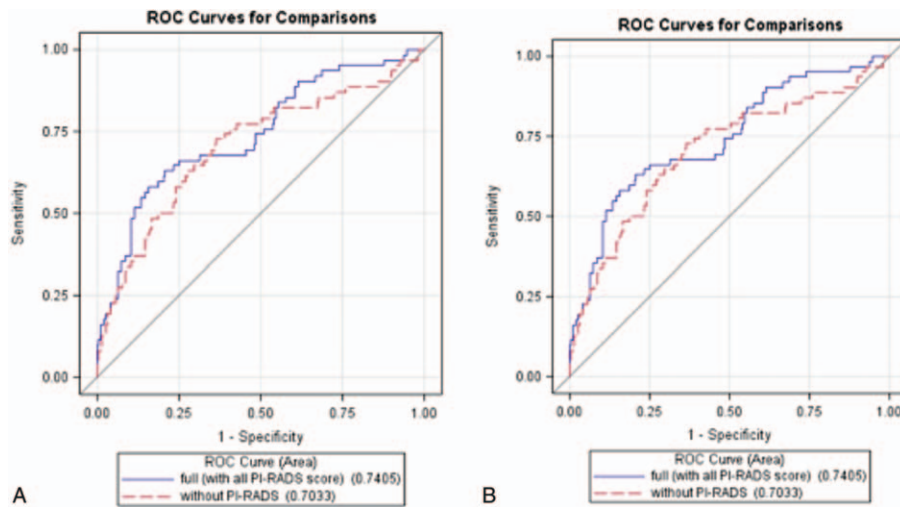
**Figure 3.** Comparison between ROC curves for pT3 for (A) all PIRADS score (P=0.12); (B) PIRADS 2–3 versus PIRADS 5 (P=0.18). PIRADS = Prostate Imaging Reporting and Data System, ROC = receiver operating characteristics.

pathology. Interestingly, these conclusions are drawn from patients who would have been otherwise classified as low-risk and so eligible for nerve-sparing surgery.

In this perspective, mpMRI could be used in combination with a variety of biomarkers, ranging from the well-known prostate cancer antigen 3 (PCA3) and 2proPSA-prostate health in-

dex[31,32] to the experimental urotensin II receptor,[33] which have been suggested to be useful tools for the reclassification of otherwise "low-risk" prostate cancers.

The present study has some limitations. First, we did not report functional outcomes and long-term oncologic follow-up. Second, our dataset did not include body mass index and

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### Table 8

**Association between the features of the patients with GS ≥7 at final pathology and PIRADS score. .**

| | Gleason Score ≥7 | | | | |
|---|---|---|---|---|---|
| | Yes N (%) | No N (%) | P value[†] | Multivariate odds ratio (95% CI) | P value |
| Age* | 63.2 (±7.3) | 61.9 (±7.0) | 0.06 | 1.01 (0.98–1.05) | 0.51 |
| Clinical stage | | | 0.10 | | 0.34 |
| cT1a-1c | 97 (75%) | 105 (84%) | | 1.00 (reference) | |
| cT2a-2c | 32 (25%) | 20 (16%) | | 1.39 (0.70–2.73) | |
| PSA* | 6.3 (±1.9) | 5.9 (±1.9) | 0.11 | 1.09 (0.95–1.25) | 0.23 |
| PIRADS | | | 0.0003[‡] | | |
| 2 | 3 (2%) | 8 (6%) | | 1.00 (reference) | |
| 3 | 14 (11%) | 31 (25%) | | | |
| 4 | 49 (38%) | 53 (43%) | | 1.96 (0.96–3.97) | 0.86 |
| 5 | 63 (49%) | 33 (26%) | | **3.47 (1.66–7.24)** | **0.002** |
| FSA | | | **<0.0001** | | **0.001** |
| Negative | 77 (60%) | 103 (82%) | | 1.00 (reference) | |
| Positive | 52 (40%) | 22 (18%) | | **2.70 (1.48–4.93)** | |
| Age* | 63.2 (±7.3) | 61.9 (±7.0) | 0.06 | 1.02 (0.98–1.05) | 0.39 |
| Clinical stage | | | 0.10 | | 0.29 |
| cT1a-1c | 97 (75%) | 105 (84%) | | 1.00 (reference) | |
| cT2a-2c | 32 (25%) | 20 (16%) | | 1.43 (0.73–2.80) | |
| PSA* | 6.3 (±1.9) | 5.9 (±1.9) | 0.11 | 1.10 (0.96–1.26) | 0.18 |
| PIRADS | | | 0.0005[§] | | **0.006** |
| 2–3 | 17 (13%) | 39 (31%) | | 1.00 (reference) | |
| 4–5 | 112 (87%) | 86 (69%) | | **2.53 (1.31–4.88)** | |
| FSA | | | **<0.0001** | | **0.0007** |
| Negative | 77 (60%) | 103 (82%) | | 1.00 (reference) | |
| Positive | 52 (40%) | 22 (18%) | | **2.81 (1.55–5.10)** | |

Univariate and multivariate analyses with PIRADS 2–3 versus 4 versus 5; PIRADS 2–3 versus 4–5. Significant ORs and P values are in bold.
* = (± SD).
[†] T test for continuous variables; $\chi^2$ test or Fisher exact test for categorical variables.
[‡] Mantel–Haenszel P value for trend: <0.0001.
[§] Mantel–Haenszel P value for trend: 0.0005.
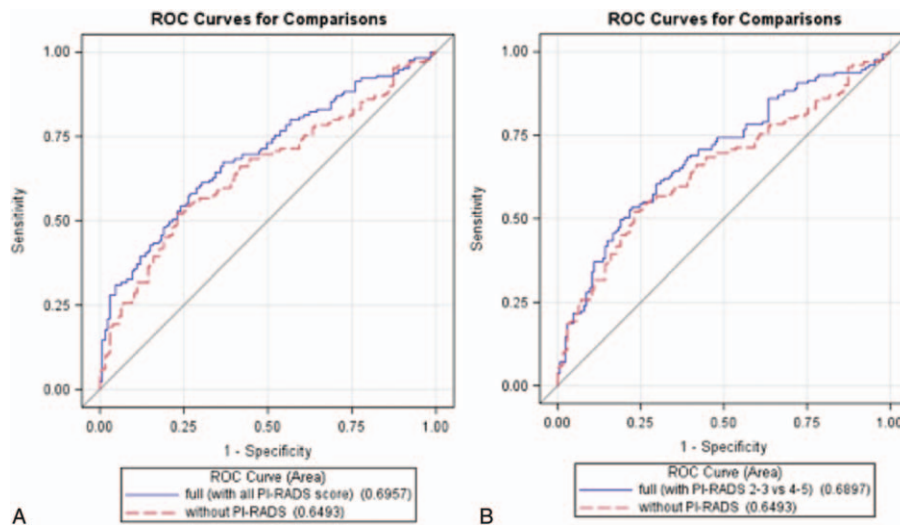
**Figure 4.** Comparison between ROC curves for GS ≥7 at final pathology with (A) all PIRADS scores ($P=0.04$); (B) PIRADS 2–3 versus PIRADS 4–5 ($P=0.03$).

prostatic volume, which can influence the incidence of PSM.[34,35] Third, we did not consider the presence of multiple lesions at mpMRI, assuming that the "index lesion" was representative of the disease as a whole. Fourth, we did not discuss the problem of costs, which are an issue when planning to perform an mpMRI for every patient with prostate cancer.

Despite these limitations, our study provided interesting results that can support the construction of new models to predict the appropriateness of a nerve-sparing procedure.

### Table 9

**Association between features of the patients and upstaging and/or upgrading[‡]: univariate and multivariate analysis with PIRADS 2–3 versus 4 versus 5; PIRADS 2–3 versus 4–5.**

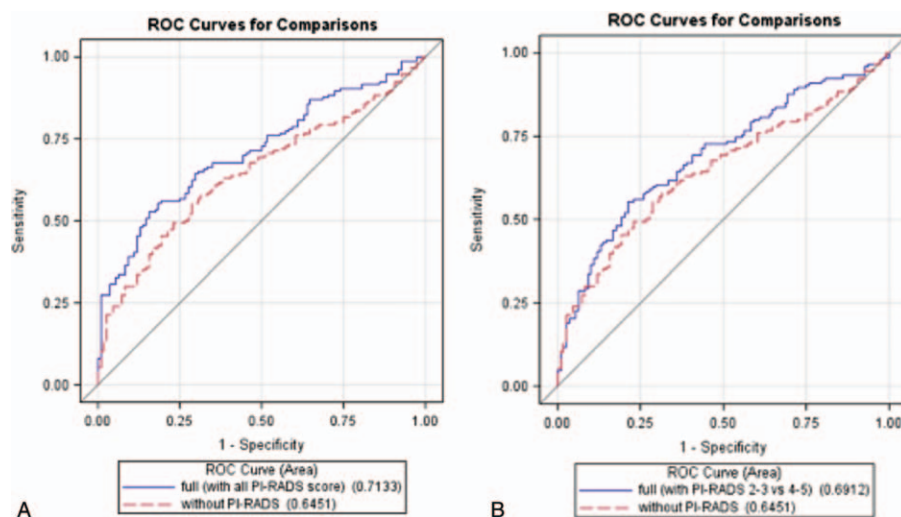| | Upstaging and/or upgrading | | | | |
|---|---|---|---|---|---|
| | Yes N (%) | No N (%) | P value[†] | Multivariate odds ratio (95% CI) | P value |
| Age* | 62.9 (±7.5) | 62.1 (±6.8) | 0.23 | 1.00 (0.96–1.04) | 0.89 |
| Clinical stage | | | 0.12 | | 0.24 |
| cT1a-1c | 110 (75%) | 92 (85%) | | 1.00 (reference) | |
| cT2a-2c | 36 (25%) | 16 (15%) | | 1.54 (0.75–3.14) | |
| PSA* | 6.2 (±2.0) | 5.9 (±1.8) | 0.26 | 1.05 (0.91–1.21) | 0.49 |
| PIRADS | | | <0.0001[§] | | |
| 2 | 3 (2%) | 8 (7%) | | 1.00 (reference) | |
| 3 | 17 (12%) | 28 (26%) | | | |
| 4 | 53 (36%) | 49 (46%) | | 1.78 (0.89–3.55) | 0.47 |
| 5 | 73 (50%) | 23 (21%) | | **4.72 (2.24–9.96)** | **<0.0001** |
| FSA | | | <0.0001 | | 0.001 |
| Negative | 89 (61%) | 91 (84%) | | 1.00 (reference) | |
| Positive | 57 (39%) | 17 (16%) | | **2.90 (1.53–5.52)** | |
| Age* | 62.9 (±7.5) | 62.1 (±6.8) | 0.23 | 1 (0.97–1.04) | 0.86 |
| Clinical stage | | | 0.12 | | 0.19 |
| cT1a-1c | 110 (75%) | 92 (85%) | | 1.00 (reference) | |
| cT2a-2c | 36 (25%) | 16 (15%) | | 1.59 (0.79–3.19) | |
| PSA* | 6.2 (±2.0) | 5.9 (±1.8) | 0.26 | 1.07 (0.93–1.23) | 0.36 |
| PIRADS | | | 0.0002[‖] | | 0.002 |
| 2–3 | 20 (14%) | 36 (33%) | | 1.00 (reference) | |
| 4–5 | 126 (86%) | 72 (67%) | | **2.70 (1.42–5.12)** | |
| FSA | | | | | 0.0005 |
| Negative | 89 (61%) | 91 (84%) | | 1.00 (reference) | |
| Positive | 57 (39%) | 17 (16%) | <0.0001 | **3.05 (1.62–5.73)** | |

Significant ORs and P values are in bold.

* = (± SD).

[†] T test for continuous variables; $\chi^2$ test or Fisher exact test for categorical variables.

[‡] Defined as GS ≥7 (upgrading) and or pathological staging >pT2 (upstaging).

[§] Mantel–Haenszel P value for trend <0.0001.

[‖] Mantel–Haenszel P value for trend 0.0002.

**Figure 5.** Comparison between ROC curves for upgrading (GS ≥7) and/or upstaging (> pT2) with (A) all PIRADS scores ($P = 0.01$); (B) PIRADS 2–3 versus 4–5 ($P = 0.02$).

## 5. Conclusions

The present study showed how mpMRI and FSA could predict upgrading, upstaging, and extraprostatic extension.

MpMRI could be part of new predictive models whose aim is to correctly classify patients preoperatively, while FSA could improve surgical strategy to obtain the best oncologic and functional outcomes.

## References

[1] Petralia G, Musi G, Padhani AR, et al. Robot-assisted radical prostatectomy: multiparametric MR imaging-directed intraoperative frozen-section analysis to reduce the rate of positive surgical margins. Radiology 2015;274:434–44.

[2] Cornud F, Flam T, Chauveinc L, et al. Extraprostatic spread of clinically localized prostate cancer: factors predictive of pT3 tumor and of positive endorectal MR imaging examination results. Radiology 2002;224:203–10.

[3] Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. Eur Radiol 2012;22:746–57.

[4] Lemaitre L, Puech P, Poncelet E, et al. Dynamic contrast-enhanced MRI of anterior prostate cancer: morphometric assessment and correlation with radical prostatectomy findings. Eur Radiol 2009;19:470–80.

[5] Futterer JJ, Heijmink SW, Scheenen TW, et al. Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. Radiology 2006;241:449–58.

[6] Tanimoto A, Nakashima J, Kohno H, et al. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. J Magn Reson Imaging 2007;25:146–52.

[7] Haider MA, van der Kwast TH, Tanguay J, et al. Combined T2-weighted and diffusion-weighted MRI for localization of prostate cancer. AJR Am J Roentgenol 2007;189:323–8.

[8] Barentsz JO, Engelbrecht M, Jager GJ, et al. Fast dynamic gadolinium-enhanced MR imaging of urinary bladder and prostate cancer. J Magn Reson Imaging 1999;10:295–304.

[9] Puech P, Potiron E, Lemaitre L, et al. Dynamic contrast-enhanced-magnetic resonance imaging evaluation of intraprostatic prostate cancer: correlation with radical prostatectomy specimens. Urology 2009;74:1094–9.

[10] Arnold M, Karim-Kos HE, Coebergh JW, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer 2015;51:1164–87.

[11] Kuru TH, Roethke MC, Rieker P, et al. Histology core-specific evaluation of the European Society of Urogenital Radiology (ESUR) standardised scoring system of multiparametric magnetic resonance imaging (mpMRI) of the prostate. BJU Int 2013;112:1080–7.

[12] Eichelberg C, Erbersdobler A, Haese A, et al. Frozen section for the management of intraoperatively detected palpable tumor lesions during nerve-sparing scheduled radical prostatectomy. Eur Urol 2006;49:1011–6.

[13] Tsuboi T, Ohori M, Kuroiwa K, et al. Is intraoperative frozen section analysis an efficient way to reduce positive surgical margins? Urology 2005;66:1287–91.

[14] Stephenson AJ, Eggener SE, Hernandez AV, et al. Do margins matter? The influence of positive surgical margins on prostate cancer-specific mortality. Eur Urol 2014;65:675–80.

[15] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.

[16] Novara G, Ficarra V, Mocellin S, et al. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. Eur Urol 2012;62:382–404.

[17] Shikanov S, Woo J, Al-Ahmadie H, et al. Extrafascial versus interfascial nerve-sparing technique for robotic-assisted laparoscopic prostatectomy: comparison of functional outcomes and positive surgical margins characteristics. Urology 2009;74:611–6.

[18] Montorsi F, Wilson TG, Rosen RC, et al. Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. Eur Urol 2012;62:368–81.

[19] Wright JL, Dalkin BL, True LD, et al. Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. J Urol 2010;183:2213–8.

[20] Sooriakumaran P, John M, Wiklund P, et al. Learning curve for robotic assisted laparoscopic prostatectomy: a multi-institutional study of 3794 patients. Minerva Urol Nefrol 2011;63:191–8.

[21] Goharderakhshan RZ, Sudilovsky D, Carroll LA, et al. Utility of intraoperative frozen section analysis of surgical margins in region of neurovascular bundles at radical prostatectomy. Urology 2002;59:709–14.

[22] Schlomm T, Tennstedt P, Huxhold C, et al. Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) increases nerve-sparing frequency and reduces positive surgical margins in open and robot-assisted laparoscopic radical prostatectomy: experience after 11,069 consecutive patients. Eur Urol 2012;62:333–40.

[23] von Bodman C, Brock M, Roghmann F, et al. Intraoperative frozen section of the prostate decreases positive margin rate while ensuring nerve sparing procedure during radical prostatectomy. J Urol 2013;190:515–20.

[24] Yu KK, Hricak H, Alagappan R, et al. Detection of extracapsular extension of prostate carcinoma with endorectal and phased-array coil MR imaging: multivariate feature analysis. Radiology 1997;202:697–702.

[25] Thompson J, Lawrentschuk N, Frydenberg M, et al. The role of magnetic resonance imaging in the diagnosis and management of prostate cancer. BJU Int 2013;112(suppl 2):6–20.

[26] Wang L, Mazaheri Y, Zhang J, et al. Assessment of biologic aggressiveness of prostate cancer: correlation of MR signal intensity with Gleason grade after radical prostatectomy. Radiology 2008;246: 168–76.

[27] Villeirs GM, De Meerleer GO, De Visschere PJ, et al. Combined magnetic resonance imaging and spectroscopy in the assessment of high grade prostate carcinoma in patients with elevated PSA: a single-institution experience of 356 patients. Eur J Radiol 2011;77:340–5.

[28] Marcus DM, Rossi PJ, Nour SG, et al. The impact of multiparametric pelvic magnetic resonance imaging on risk stratification in patients with localized prostate cancer. Urology 2014;84:132–7.

[29] McClure TD, Margolis DJ, Reiter RE, et al. Use of MR imaging to determine preservation of the neurovascular bundles at robotic-assisted laparoscopic prostatectomy. Radiology 2012;262:874–83.

[30] Hricak H, Wang L, Wei DC, et al. The role of preoperative endorectal magnetic resonance imaging in the decision regarding whether to preserve or resect neurovascular bundles during radical retropubic prostatectomy. Cancer 2004;100:2655–63.

[31] De Cobelli O, Buonerba C, Terracciano D, et al. Urotensin II receptor on preoperative biopsy is associated with upstaging and upgrading in prostate cancer. Future Oncol 2015;11:3091–8.

[32] Lucarelli G, Rutigliano M, Galleggiante V, et al. Metabolomic profiling for the identification of novel diagnostic markers in prostate cancer. Expert Rev Mol Diagn 2015;15:1211–24.

[33] Ferro M, Lucarelli G, Bruzzese D, et al. Improving the prediction of pathologic outcomes in patients undergoing radical prostatectomy: the value of prostate cancer antigen 3 (PCA3), prostate health index (phi) and sarcosine. Anticancer Res 2015;35:1017–23.

[34] Campeggi A, Xylinas E, Ploussard G, et al. Impact of body mass index on perioperative morbidity, oncological, and functional outcomes after extraperitoneal laparoscopic radical prostatectomy. Urology 2012;80: 576–84.

[35] Knoedler JJ, Karnes RJ, Thompson RH, et al. The association of tumor volume with mortality following radical prostatectomy. Prostate Cancer Prostatic Dis 2014;17:144–8.