Role of magnetic resonance imaging for preoperative prediction of early biochemical failure in localized prostate cancer

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Background: The purpose of our study was to assess preoperative clinical biological and Magnetic Resonance Imaging (MRI) predictive factors of early biochemical failure (BF), defined as persistence of significant post-operative plasmatic prostate specific antigen (PSA) level after radical prostatectomy (RP) in patients with localized prostate cancer (PCa).

Methods: In a retrospective cohort study we included 142 patients from our university hospital with newly diagnosed PCa, who underwent 3T multiparametric MRI prior to RP. Only the MRI target lesions [Prostate Imaging Reporting and Data System (PIRADS) ≥3] with histological correspondence were considered significant. Clinical, biological, MRI and pathological preoperative data were studied. We performed univariate and multivariate logistic regression analysis to identify significant parameters associated with early BF.

Results: Early BF occurred in 14% of patients (20/142). Patients with BF had higher PSA level at diagnosis, Gleason score, number of positive biopsies, size of the largest positive biopsy and higher National Comprehensive Cancer Network (NCCN) risk score (P<0.001 for all). According to MRI, they also had higher T stage and a higher size of capsular contact (P<0.001 for all). In contrast, there was no difference concerning neither ADC value, perfusion profile and zonal location of the index lesion. In multivariate analysis, the best combination of predictive factors of early BF was the association of preoperative Gleason score ≥4+3 [odds ratio (OR) =6.8 (1.4–32.5); P=0.002] and T stage ≥3 on preoperative MRI [OR =17.4 (3.2–94.9); P<0.001] with an area under the curve (AUC) of 0.89 [99% confidence interval (CI): 0.77–1], a negative predictive value of 94% and a positive predictive value of 75%.

Conclusions: Combination of simple preoperative biomarkers as Gleason score and T stage according to MRI accurately stratify the risk of early BF following RP. These results emphasize the pivotal role of preoperative MRI for the management of localized PCa.

Keywords: Prostate cancer (PCa); magnetic resonance imaging (MRI); radical prostatectomy; post-operative prostate specific antigen (post-operative PSA); biochemical failure (BF)

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Introduction

The standard care of localized prostate cancer (PCa) relies on surgery, external radiotherapy or brachytherapy. Radical prostatectomy (RP) remains the most common treatment for patients with life expectancy >10 years (1). However, biochemical recurrence at 10 years following RP goes up to 40% (with an associated mortality rate of 6%) (1), and RP can have specific complications (such as incontinence and erectile dysfunction) (2). For these reasons, selection of patients before RP appears essential. This selection is based on D'Amico or National Comprehensive Cancer Network (NCCN) risk classifications, combining histological aggressiveness (Gleason score), anatomical extension [(with digital rectal examination (DRE) or magnetic resonance imaging (MRI)] and PSA level (1).

Multi-parametric MRI (mpMRI) of the prostate is used to optimize cancer detection [Prostate Imaging Reporting and Data System (PIRADS) 2.1 standardized criteria] (3,4), for therapeutic decision guidance and research of local recurrence after curative treatment (5,6). Several MRI prognostic factors are already related with cancer recurrence: PIRADS score (7), apparent diffusion coefficient (ADC) value (8-10), extra-prostatic extension, invasion of seminal vesicles, size of the lesion or apical location (before radiotherapy) (11). Dynamic acquisition also provides useful information for tumor detection and characterization (12).

Plasmatic PSA level is expected to be undetectable within 6 weeks after successful RP (13). Persistently measurable plasmatic PSA in patients following RP is considered as an early biochemical failure (BF) (residual cancer in relation with micrometastases or residual disease in the prostatic fossa). High PSA velocity and unfavorable pathological characteristics tend to point to metastatic disease (1). Nevertheless, no consensus exists, and the majority of patients are treated by salvage radiotherapy alone (1). The recurrence-free survival rate at 5 years is low at 22% but survival in this patient group remains high (95% at 5 years) (1).

Predictive factors of early BF are scarcely described in the literature but are close to those exposed for later recurrence: pre-operative (Gleason score, clinical T stage, body mass index) and pathologic criteria (post-operative stage, extra-prostatic extension, lymph node positivity, positive surgical margin and tumor volume) (8,14,15).

However, there is limited knowledge regarding mpMRI predictive factors of early BF.

The aim of our study was to evaluate the preoperative predictive factors of early BF after RP in patients with localized PCa, including clinical, biological, pathological and especially mpMRI factors in order to predict the effectiveness of prostatectomy. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-472/rc).

Methods

Selection of patients

In an observational retrospective cohort study we selected between December 2012 and June 2018 756 patients underwent RP in the University Hospital of Dijon (France) for initial treatment of localized newly diagnosed PCa. Inclusion dates were linked to a database of prostatectomies in our urology department, we searched for corresponding MRIs. From this database, we retrospectively selected patients who had the following inclusion criteria:

- ❖ PCa histologically proven by transrectal ultrasound guided biopsy: [at least 12 systematic biopsies more or less a few targeted biopsies (1 to 3) depending on the DRE, ultrasound or MRI].
- ❖ Curative treatment by RP ± lymph node dissection (1) after a collegial decision. For patients with intermediate or high risk, staging was performed using CT and bone scintigraphy (1).
- ❖ A 3T multiparametric MRI performed in our center before treatment.

Patients were not included if they had one of the following criteria:

- ❖ Gleason score <6 on the pathological surgery report.
- ❖ A history of PCa or any prostate surgery.
- ❖ Lymph node involvement or distant metastasis on initial assessment.
- ❖ An initially uncontrolled disease (PSA level detectable despite adjuvant radiotherapy which reflected a probable non-localized disease).
- ❖ Poor mpMRI quality (prostate bleeding, metal artifacts mainly related to total hip prosthesis,
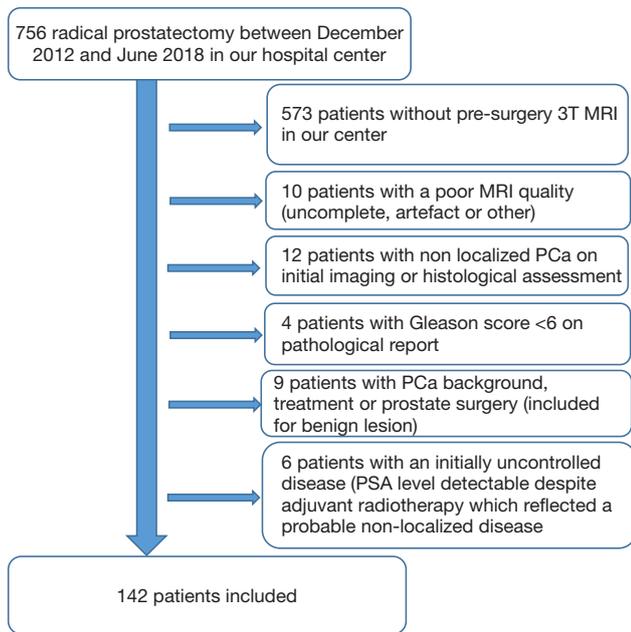
Figure 1 Flow chart. MRI, magnetic resonnance imaging; PCa, prostate cancer; PSA, prostate specific antigen.

Table 1 MRI protocol

Parameters	T2-weighted	DWI	DCE
Orientation	3 planes	Axial	Axial
TR (ms)	3,600	4,200	3, 25
TE (ms)	75	101	1, 12
Slice thickness (mm)	3, 5	3, 5	3, 5
FOV (mm)	280	240	280
B value (s/mm^2)	NA	0, 100, 800	NA
Temporal resolution (s)	NA	NA	6
Total observation time (s)	NA	NA	240

MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; DCE, dynamic contrast-enhanced on T1 fat sat gadolinium sequence; TR, repetition time; TE, echo time; FOV, field of view.

patient movement or digestive gas, incomplete MRI) or MRI performed in another imaging center.

Following this selection process, we identified 142 patients. A flow chart was attached (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study obtained ethical approval from the Institutional Review Board of the University Hospital of Dijon (France) and individual consent for this retrospective analysis was waived.

MRI technique and data

All patients underwent MRI on a 3 Tesla magnet (Trio Tim, Siemens Healthcare) with a pelvic antenna (9). The sequences of examination mainly included T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging.

Table 1 summarizes the MRI protocol for imaging of the prostate gland. All MRI images were archived using a PACS system (GE Healthcare).

MRI data analysis

Data analysis was performed using the Image J software. All MR images were retrospectively reviewed by a trained radiologist (not blinded from the initial report). An example of an MRI tumour lesion is attached in *Figure 2*.

Global prostate data were assessed: prostate volume, ADC value in healthy prostate (transition and peripheral zone), and wash-in calculation (directing coefficient of the ascending slope) from DCE-MRI in healthy prostate.

Each intraprostatic lesion was classified according to the PIRADS algorithm V2.0. The topography and number of significant (PIRADS ≥3) lesions were reported. If more than one significant lesion was present, the index lesion was defined as the one with the highest PIRADS score and the largest diameter. Targets in anterior fibromuscular stroma (AFMS) were then analyzed with transition zone targets.

For the index lesion the following data were assessed: largest diameter (on axial T2 sequence), location, capsular contact (measured along the perimeter of the prostate to avoid a linear distance), tumor wash-in, tumor perfusion curve, ADC value [average region of interest (ROI) including the whole lesion and calculated average of the 10% of the lowest values] and MRI T stage was defined. To estimate presence of an extra-capsular extension (ECE) readers used Likert scale and the European Society of Urogenital Radiology (ESUR) criteria (1).

Clinical, biological and pathological data

Data and medical history were extracted using DxCare software. Clinical and pathological data were:

    ❖ Age at diagnosis.
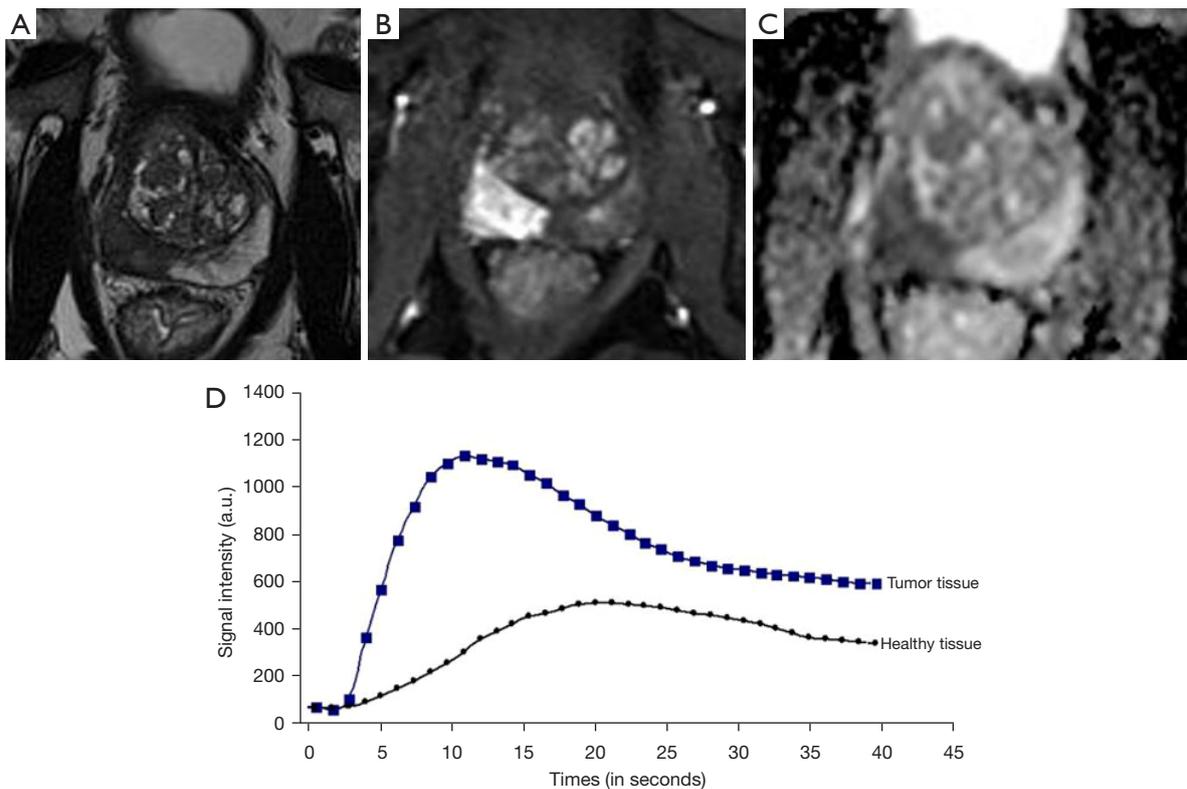
Figure 2 Example of a PZ target lesion. (A) Axial T2. (B) DCE. (C) ADC. (D) Signal versus time curve (type 3, pathological area versus healthy area). A 62-year-old man with abnormal digital rectal exam (T2b), PSA plasma level at 13 ng/mL and Gleason score 4+4. PCa in 8 of 14 cores on transrectal ultrasound-guided biopsies. Axial T2-weighed image showed a PIRADS 5 lesion, measured tumor capsular contact length was 30 mm and MRI extracapsular extension has been suspected then confirmed after surgery. This patient was in the early BF group. a.u., arbitrary units; PZ, peripheral zone; DCE, dynamic constrast-enhanced; ADC, apparent diffusion coefficient; PSA, prostate specific antigen; PCa, prostate cancer; PIRADS, Prostate Imaging Reporting and Data System; MRI, magnetic resonnance imaging; BF, biochemical failure.

- ❖ Time interval between diagnosis and surgery and between MRI and surgery.
- ❖ Clinical T stage (DRE).
- ❖ Pre-therapeutic and post-surgery PSA plasma level (before and 6 weeks after surgery, any significant PSA level was confirmed at 3 months).
- ❖ Any adjuvant treatment (radiotherapy or hormone therapy).
- ❖ Data related to biopsies: Gleason score/number of positive biopsies/size of the largest positive biopsy (cancer core length)/MRI performed prior to biopsies or not.
- ❖ Data from RP pathological report: prostate weight/ number of cancer focus/tumor size/Gleason score/ T stage/lymph node dissection and if applicable presence or not of lymph node invasion/ECE/ invasion of seminal vesicles/surgical margin.

Other elements have been extrapolated:
- ❖ For each cancer described on pathological report: topographic concordance with MRI and biopsies.
- ❖ Staging according to NCCN classification. Three variants of this score were determined: the common clinical version (including PSA level, DRE T stage and biopsy Gleason score), the MRI-based version (MRI stage instead of clinical stage) and the pathological version (stage and Gleason of the prostatectomy pathological report).

Follow-up data

Follow-up data were annual PSA level, date of recurrence, survival status and effective follow-up duration in months.

At least annual consultation with a urologist from our center was scheduled. Otherwise, the patient was followed

Table 2 Analysis of correlation between independent variables

	Pearson correlation coefficient							
	GS	NPB	BCL	Clinical NCCN	MRI NCCN	MLCC	MTS	MRI T stage
GS	1.00000; –; 142	0.29046; 0.0005; 142	0.41429; <0.0001; 142	0.78709; <0.0001; 142	0.64433; <0.0001; 142	0.30134; 0.0008; 123	0.24629; 0.0044; 132	0.34779; <0.0001; 142
NPB	0.29046; 0.0005; 142	1.00000; –; 142	0.59218; <0.0001; 142	0.47213; <0.0001; 142	0.43468; <0.0001; 142	0.43092; <0.0001; 123	0.39133; <0.0001; 132	0.38795; <0.0001; 142
BCL	0.41429; <0.0001; 142	0.59218; <0.0001; 142	1.00000; –; 142	0.53712; <0.0001; 142	0.51830; <0.0001; 142	0.39425; <0.0001; 123	0.43469; <0.0001; 132	0.46064; <0.0001; 142
Clinical NCCN	0.78709; <0.0001; 142	0.47213; <0.0001; 142	0.53712; <0.0001; 142	1.00000; –; 142	0.76257; <0.0001; 142	0.37612; <0.0001; 123	0.34573; <0.0001; 132	0.41589; <0.0001; 142
MRI NCCN	0.64433; <0.0001; 142	0.43468; <0.0001; 142	0.51830; <0.0001; 142	0.76257; <0.0001; 142	1.00000; –; 142	0.51227; <0.0001; 123	0.57324; <0.0001; 132	0.79835; <0.0001; 142
MLCC	0.30134; 0.0008; 121	0.43092; <0.0001; 121	0.39425; <0.0001; 121	0.37612; <0.0001; 121	0.51227; <0.0001; 121	1.00000; –; 123	0.79728; <0.0001; 121	0.57213; <0.0001; 121
MTS	0.24629; 0.0044; 132	0.39133; <0.0001; 132	0.43469; <0.0001; 132	0.34573; <0.0001; 132	0.57324; <0.0001; 132	0.79728; <0.0001; 123	1.00000; –; 132	0.63766; <0.0001; 132
MRI T stage	0.34779; <0.0001; 142	0.38795; <0.0001; 142	0.46064; <0.0001; 142	0.41589; <0.0001; 142	0.79835; <0.0001; 142	0.57213; <0.0001; 123	0.63766; <0.0001; 132	1.00000; –; 142

0.29046: Pearson correlation coefficient; 0.0005: confidence interval; 142: population covered by the analysis. GS, Gleason score on biopsies; NPB, number of positive biopsies; BCL, biopsy core length in mm; NCCN, National Comprehensive Cancer Network; MRI, magnetic resonance imaging; MLCC, MRI length of capsular contact in mm; MTS, MRI tumor size in mm.

by his general practitioner and referred to the urologist if necessary. For patients with a follow-up less than 5 years in our database, the investigator attempted to know the recurrence's status in 2020 by contacting the patient's general practitioner.

Statistical analysis

Qualitative data were described using number (percentage) and quantitative data using median and [interquartile range]. Patients were categorized according to absence or presence of early BF, defined as a PSA level >0.10 ng/mL 6 weeks after surgery (16). For continuous variables, comparisons were performed after testing for variances homogeneity, test used depending on the normality of the distribution.

In detail, we used Wilcoxon test for age, PSA level, time between biopsies and surgery, number of positive biopsies, biopsy core length, time between MRI and surgery, MRI prostate volume, PSA density, MRI tumor size, length of MRI capsular contact, MRI wash in and postoperative index lesion size, We used Fisher test for clinical T stage, biopsies Gleason score, clinical NCCN, number of MRI lesions, MRI T stage, NCCN MRI risk, MRI tumor location,

presence of an MRI capsular contact, postoperative number of lesions, postoperative Gleason score, postoperative T stage, postoperative NCCN risk, postoperative lymph node invasion and postoperative invasion of seminal vesicles. We used Student t-test for ADC values, the Kruskal-Wallis test for prostate weight and the Chi-square test for MRI performed before biopsies or not, PIRADS score, MRI perfusion curve, surgical lymph node dissection, postoperative ECE and post-operative margins. The χ^2 test or the Fisher exact test was used for categorical variables. Finally, we add in *Table 2* the analysis of correlation between independent variables. We recall that P tests the correlation coefficient against 0, i.e., two variables are correlated if the result is greater than 0.5.

Logistic regression analysis was performed to test for predictors of early BF. All variables were tested by univariate analysis. Because of the small number of events, only variables with a P value less than 0.01 in univariate analysis were selected for the multivariate analysis. Odds ratio (OR) were presented with their 99% confidence interval (99% CI). All the tests were 2-sided and a P value <0.01 was considered significant. Analyses were performed using SAS software version 9.4.

Table 3 Preoperative clinical and biological characteristics of patients

Parameter	All patients (n=142)	No early BF (n=122)	Early BF (n=20)	P	Test
Age (years)	65 [61–68]	64 [60–67]	66 [63–69]	0.21	Wilcoxon
PSA (ng/mL)	7.3 [5.6–9.6]	7.1 [5.5–9.0]	9.3 [7.4–14.5]	<0.001	Wilcoxon
Clinical T stage				0.24	Fisher
T1c	73	66	7		
T2a	45	38	7		
T2b	16	12	4		
T2c	6	5	1		
T3a	2	1	1		
Time between biopsies and surgery (months)	3.5 [2.4–4.4]	3.5 [2.4–4.6]	3.0 [2.3–4.3]	0.18	Student
Gleason score				<0.001	Fisher
3+3	63	60	3		
3+4	47	43	4		
4+3	16	9	7		
4+4	10	6	4		
>4+4	6	4	2		
Number of positive biopsies	4.0 [2.0–6.0]	4.0 [2.0–6.0]	6.0 [4.0–9.0]	<0.001	Student
Biopsy core length (mm)	7.0 [4.0–10.0]	6.5 [4.0–10.0]	10.5 [7.5–13.5]	<0.001	Student
Clinical NCCN risk classification				<0.001	Fisher
(Very) low risk	40	38	2		
Intermediate favorable	40	38	2		
Intermediate unfavorable	42	32	10		
(Very) high	20	14	6		

Results are expressed as number for categorical variables and median [interquartile range] for continuous variables. BF, biochemical failure; PSA, prostate specific antigen; NCCN, National Comprehensive Cancer Network.

Results

Characteristics of patients

Preoperative clinical and biological characteristics of patients are reported in *Table 3*. The topographical concordance of the biopsies with pathological data was 84% (103/122 patients) in no early BF group versus 95% (19/20 patients) in early BF group (P=0.31).

Patients with early BF had higher preoperative PSA level, Gleason score according to biopsies, number of positive biopsies, tumor biopsy core length and higher NCCN risk (P<0.001 for all). In contrast, there was no difference among the groups concerning age, time interval between diagnosis and surgery and clinical T stage.

Preoperative MRI

Preoperative MRI data are reported in *Table 4* (global characteristics) and *Table 5* (index lesion characteristics).

In most of the patients (109, 77%), diagnostic biopsies were performed before MRI. The topographical concordance of MRI with pathological data was 88% (125 patients) with 105 patients (86%) in no early BF group and 20 patients (100%) in early BF group. Ten (7%) of the 142 patients didn't have target lesion visible on MRI, none of them were in the early BF group. There was no difference among the groups concerning all these parameters.

MRI T stage and MRI NCCN risk classifications were

Table 4 Preoperative MRI parameters (global characteristics)

Parameter global characteristics (n=142)	All patients (n=142)	No early BF (n=122)	Early BF (n=20)	P	Test
Time interval between MRI and surgery (months)	2.6 [1.4–4.1]	2.6 [1.4–4.1]	2.6 [1.3–4.3]	0.86	Fisher
MRI performed before biopsies	33 (23.2%)	25 (20.5%)	8 (40.0%)	0.08	Fisher
Prostate volume (mm³)	45 [35–62]	43 [34–61]	55 [46–66]	0.05	Wilcoxon
PSA density	0.13 [0.10–0.18]	0.13 [0.09–0.17]	0.16 [0.12–0.27]	0.05	Wilcoxon
Number of lesions				0.26	Fisher
0	10	10	0		
1	106	92	14		
2	22	17	5		
3	4	3	1		
MRI T stage				<0.001	Fisher
T2a	44	43	1		
T2b	8	8	0		
T2c	42	39	3		
T3a	22	16	6		
T3b	15	5	10		
T4	1	1	0		
MRI NCCN risk classification				<0.001	Fisher
(Very) low	28	28	0		
Intermediate favorable	23	22	1		
Intermediate unfavorable	42	40	2		
(Very) high	49	32	17		

Results are expressed as number or number (percentage) for categorical variables and median [interquartile range] for continuous variables. MRI, magnetic resonance imaging; BF, biochemical failure; PSA, prostate specific antigen; NCCN, National Comprehensive Cancer Network.

significantly different among the groups (P<0.001 for both). Ten out of 20 patients (50%) in early BF group had a seminal vesicles invasion on MRI (stage 3b) versus 5 out of 112 patients (4.5%) in the other group.

There were 157 target lesions identified in 132 patients. The MRI lesion index was most often localized in the peripheral zone [97 out of 132 patients (73.5%)]. A PIRADS 5 score was most frequently found for the index lesion (78 patients–59 %). Most of the target lesions had a capsular contact (n=123; 93%), the prevalence of these last criteria weren't significantly different between our groups. There was also no significant difference for the median ADC value of the index lesion (P=0.06), the mean value of the lowest 10% ADC (P=0.22), neither for the ratio ADC target lesion/healthy prostate (P=0.06). There was no

difference either concerning DCE-MRI parameters such as wash-in coefficient (P=0.09) or type of perfusion curve (P=0.96). Only two MRI parameters of the index lesion were significantly different among the groups: the length of the capsular contact and the tumor size that were longer for patients with early BF (P<0.001 for both).

Postoperative pathological data

Postoperative pathological data are reported in *Table 6*.

There were 254 tumor lesions in our 142 patients, many of MRI unseen foci were subcentimetric with a Gleason score ≤3+3 (87 out of the 97 unseen tumor foci). Between 1 and 4 tumor foci were identified by patients. There was no significant difference among the groups concerning these

Table 5 Preoperative MRI data (index lesion characteristics)

Parameter index lesion characteristics (n=132)	All patients (n=132)	No early BF (n=112)	Early BF (n=20)	P	Test
PIRADS V 2.0				0.03	Chi-Square
3	4	4	0		
4	50	47	3		
5	78	61	17		
Tumor location				0.24	Fisher
Peripheral zone	97	79	18		
Central zone	32	30	2		
Anterior fibro-muscular stroma	3	3	0		
Tumor size (mm)	16 [12–21]	15 [11–21]	20 [14–37]	<0.001	Wilcoxon
Capsular contact (yes)	123 (93.2%)	103 (92.0%)	20 (100.0%)	0.35	Fisher
Length of capsular contact (mm)	13 [9–18]	12 [9–16]	21 [15–38]	<0.001	Wilcoxon
ADC value (mm^2/s)	808 [701–933]	826 [713–936]	760 [636–860]	0.06	Student
Average of the lowest 10% of ADC's value (mm^2/s)	591 [453–742]	602 [468–747]	566 [409–679]	0.22	Student
Ratio ADC lesion/ADC healthy area	0.5 [0.4–0.6]	0.6 [0.5–0.6]	0.5 [0.4–0.6]	0.06	Student
Wash in coefficient	200 [156–267]	197 [152–259]	222 [190–272]	0.09	Student
Type of perfusion curve				0.96	Chi-Square
1	6	5	1		
2	43	36	7		
3	83	71	12		

Results are expressed as number or number (percentage) for categorical variables and median [interquartile range] for continuous variables. MRI, magnetic resonance imaging; BF, biochemical failure; PIRADS, Prostate Imaging Reporting and Data System; ADC, apparent diffusion coefficient.

criteria. Patients with early BF more frequently had lymph node involvement (P<0.001—11 out of 20 early BF with proven lymph node involvement).

As with the pre-operative data, Gleason score/T stage/ NCCN risk and the size of the main tumor focus were also higher in patients with early BF (P<0.001 for all). Pathological ECE, surgical margin (R1) and seminal vesicle invasion were also significantly higher (P<0.001).

Post-operative data and follow-up

Following surgery, 33 patients received adjuvant treatment including all patients in the early BF group and 13 patients in no early BF group. Twelve patients received only radiotherapy, 2 only hormone therapy and 19 both treatments [including 15 patients (75%) in early BF group] after a collegial decision. In the early BF

group, the median PSA level 6 weeks after surgery was 0.48 (0.19–1.21) ng/mL.

The median follow-up time was 62.7 (29.6–79.4) months with 79 patients (56%) with an effective follow-up >5 years. No death related to PCa was observed. At the end of the follow-up, a total of 30 patients (21%) had recurrence of their PCa including 9 (45%) in the early BF group (P=0.014). Time before recurrence was 39 (25.0–60.0) months without significant difference between groups.

Predictive factors of early BF

Logistic regression analysis was performed to determine predictive factors of early BF. All parameters listed in *Tables 4,5* were tested by univariate analysis. Significant criteria were:

❖ Gleason score ≥4+3: OR =9.6 (2.5–36.8); P<0.001;

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Table 6 Postoperative pathological data

Parameter	All patients (n=142)	No early BF (n=122)	Early BF (n=20)	P	Test
Prostate weight (g)	55 [46–71]	54 [46–70]	57 [52–80]	0.10	Wilcoxon
Number of lesions				0.23	Fisher
1	57	49	8		
2	59	52	7		
3	25	21	4		
4	1	0	1		
Gleason score				<0.001	Fisher
3+3	20	19	1		
3+4	81	78	3		
4+3	21	13	8		
4+4	13	8	5		
>4+4	7	4	3		
Pathological T stage				<0.001	Fisher
T2a	17	17	0		
T2b	1	1	0		
T2c	67	64	3		
T3a	36	31	5		
T3b	20	9	11		
T4	1	0	1		
Pathological NCCN classification				<0.001	Fisher
(Very) low	4	4	0		
Intermediate favorable	19	18	1		
Intermediate unfavorable	55	53	2		
(Very) high	64	47	17		
Lymph node dissection	60 (42.3)	44 (36.1)	16 (80.0)	<0.001	Chi-Square
Lymph node invasion proven by histology	13 (21.7)	2 (4.5)	10 (50.0)	<0.001	Fisher
Size of the index lesion (mm)	22 [16–28]	20 [16–26]	35 [28–46]	<0.001	Student
ECE				<0.001	Chi-Square
Not invaded	39	39	0		
Invaded not exceeded	48	45	3		
Invaded exceeded	55	38	17		
Invasion of seminal vesicles	21 (14.8)	9 (7.4)	12 (60.0)	<0.001	Fisher
Margins				<0.001	Chi-Square
R0	104	97	7		
R1	38	25	13		

Results are expressed as number or number (percentage) for categorical variables and median [interquartile range] for continuous variables. BF, biochemical failure; NCCN, National Comprehensive Cancer Network; ECE, extra-capsular extension.
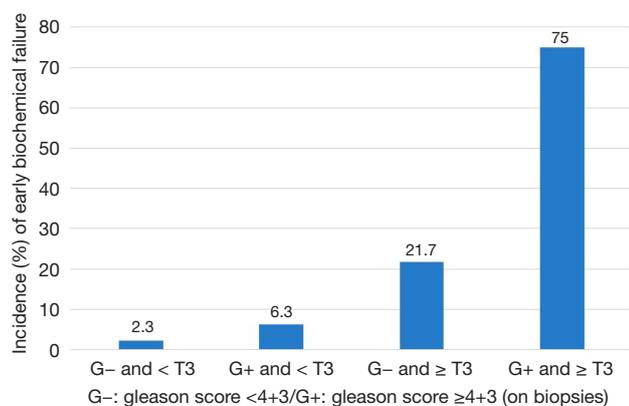
Figure 3 Incidence (%) of early BF according to absence or presence of Gleason score ≥4+3 and MRI T stage ≥3. BF, biochemical failure; MRI, magnetic resonance imaging.

AUC =0.75.
- ❖ Tumor biopsy core length >7 mm: OR =4.3 (1.1–17.1); P=0.006; AUC =0.71.
- ❖ Clinical NCCN ≥ intermediate unfavorable: OR =6.0 (1.4–26.0); P<0.002; AUC =0.71.
- ❖ MRI NCCN ≥ high risk: OR =13.9 (2.8–69.5); P<0.001; AUC =0.79.
- ❖ MRI T stage ≥3: OR =22.3 (4.4–114.5); P<0.001; AUC =0.83.
- ❖ Size of capsular contact >20 mm: OR >8.7 (2.1–36.3); P<0.001; AUC =0.70.

Pre-surgery PSA level (thresholds of 10 or 20 ng/mL as used in NCCN classification), having at least 4 positive biopsies, a cut off at 17 mm for index lesion size or a cut off at 10 mm for capsular contact length were not significant [whereas the cut off at 20 mm (16) was significant].

For multivariate analysis we tested pairwise combinations of pre-operative, MRI or mixed data. Only relevant analyses are reported (P<0.01/AUC >0.80):
- ❖ Gleason ≥4+3 and capsular contact length >20 mm: OR =6.6 (1.6–28.3) and 6.3 (1.3–29.7)/P<0.001 and P=0.002/AUC =0.80 (99% CI: 0.64–0.95).
- ❖ Gleason ≥4+3 and MRI T stage ≥3: OR 6.8 (1.4–32.5) and 17.4 (3.2–94.9)/P=0.002 and P<0.001/AUC =0.89 (99% CI: 0.77–1.00).
- ❖ NCCN IRM ≥ high risk and capsular contact length >20 mm: OR =8.1 (2.2–106.3) and 4.82 (1.1–22.7)/P=0.001 and P=0.009/AUC =0.83 (99% CI: 0.69–0.96).

The best association for prediction of a radical prostatectomy early BF was preoperative Gleason score ≥4+3 and MRI T stage ≥3. Presence of these two factors permitted to predict early BF after RP with a sensitivity of 60%, a specificity of 97%, a positive predictive value of 75%, a negative predictive value of 94%, and an accuracy of 91% (*Figure 3*).

Discussion

RP remains the treatment of choice for eradication of localized PCa. A high risk of extra-prostatic extension is a usual contraindication for nerve sparing. European Association of Urology (EAU) has established guidelines for the evaluation of tumor extension before RP, recently updated (17), mpMRI may be helpful for selecting a nerve-sparing approach because it has good specificity but low sensitivity for detecting pT3a stages. Previous studies have shown the interest of mpMRI for prediction of recurrence following RP (10,11,18). By focusing on prediction of persistence of detectable post-operative PSA, defined in our study as early BF, our result emphasizes the crucial role of mpMRI before RP. In addition to Gleason score on biopsies, MRI capsular contact length and MRI T stage confirm their major role in post-operative PSA significant level prediction.

Indeed, the combination of significant cancer on biopsy (Gleason ≥4+3) and suspected extracapsular extension/seminal vesicle invasion (stage ≥ T3a) is 75% predictive of incomplete surgery (80% for the combination of Gleason score and capsular contact >20 mm), all with negative predictive values >90%. A multivariate prognostic score combining these different factors should be refined by a larger cohort in order to predict the effectiveness of surgery especially since patients with early BF have a high risk of recurrence and progression disease. A potential predictive MRI/Gleason score could counter-indicate RP in patients identified at high risk of early BF, avoiding surgical complications and directing patients to alternative treatment (radiotherapy and/or hormone therapy).

The distribution of index lesions didn't show any topographical predominance outside the usual distribution of cancers between peripheral zone (about 70%) and transition zone (about 30%) (1) in contrast to other studies (14). The number of target lesions on MRI didn't influence the risk of early BF. The patient's prognosis appears to be largely driven by the index lesion in the case of a RP.

T3 or higher suspected T-stage on MRI is the best threshold to predict early PSA failure despite the relative subjectivity of ECE on MRI. Pathological analysis and MRI

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bring an up-staging of NCCN classification compared to clinical data as in other studies (19). The size of the target lesion is also associated with the risk of early BF.

In our study, PIRADS score is not associated with the risk of early BF, in contrast to its well-established role for prediction of recurrence (20) and characterization of malignant lesions (21). Our data also shows a limit of significance of the target/healthy area ADC ratio, despite the interest of ADC value in detecting significant lesions and the estimation of the aggressiveness having already been demonstrated (4,22). Others ADC data weren't significant. Similarly, evaluation of perfusion parameters (wash-in and type of perfusion curve) weren't predictors of early BF in our study, despite the role of quantitative perfusion in the prediction of significant lesion/tumor aggressiveness (5,23).

In contrast, the length of the capsular contact is one of the most interesting MRI data for prediction of early BF. We studied 2 cut offs: the commonly used 10 mm threshold and 20 mm according to the recent study by Mendez *et al.* (24). A threshold of 20 mm seems more relevant than 10 mm to predict an early BF (50% of patients in group 2 for 20 mm). Definition of significant capsular contact should be redefined in the future. According to our results, it is clear that mpMRI improves the tumor T classification and modifies the prognostic of PCa even if it remains dependent and limited by the radiologist's experience.

The functional parameters of the index tumor (such as ADC value or perfusion profile), which help to characterize its aggressiveness, are interesting markers of the risk of recurrence, but fail in our study to predict early BF following RP.

According to the literature, Gleason score is associated with ADC value. In our study, the ADC is at the limit of significance (P=0.06) probably due to the small study population.

In contrast, our results confirm that the morphological characteristics of the index tumor (size of the lesion, length of capsular contact, presence of an ECE) are more relevant in predicting early BF.

Our study has several limitations. The sample size, as well as the retrospective nature of this single institution study, limits the generalizability of our results. The majority of the biopsies weren't directed by a prior MRI. This common practice during the patient inclusion period is no longer recommended nowadays according to the superiority of mpMRI associated with targeted biopsies for the detection of significant cancers (25). Our MRI detection sensitivity could have been reduced because of these

conditions. Furthermore, we are not able to ensure that patients with early BF did not have metastatic or lymphatic disease prior to surgery (despite our exclusion criteria).

Conclusions

Combination of preoperative Gleason score and T stage based on mpMRI permits to predict persistence of detectable PSA (early BF) following RP for patients with localized PCa, with a high accuracy (positive predictive value of 75% and negative predictive value of 94%). These results highlight the major importance of mpMRI in the initial staging of PCa, for lesion detection but also for prognostic stratification, in order to optimize therapeutic strategies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-472/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-472/coif). AC serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*; RL serves as an unpaid deputy editor of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethcial Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study obtained ethical approval from the Institutional Review Board of the University Hospital of Dijon (France) and individual consent for this retrospective analysis was waived.

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