Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

**ANNÉE 2021**

N°

# FACTEURS PRÉDICTIFS PRÉ-OPÉRATOIRES DE L'ÉCHEC BIOLOGIQUE PRÉCOCE DANS LE CANCER DE LA PROSTATE LOCALISÉ APRÈS PROSTATECTOMIE RADICALE

# PREOPERATIVE PREDICTIVE FACTORS OF EARLY BIOCHEMICAL FAILURE IN LOCALIZED PROSTATECANCER AFTER RADICAL PROSTATECTOMY

**THÈSE**

Présentée

à l'UFR des Sciences de Santé de Dijon

Circonscription Médecine

et soutenue publiquement le jeudi 15 avril 2021

pour obtenir le grade de Docteur en Médecine

Par Monsieur Jérémy CASSIN

Né le 07/09/1991

À Neufchâteau (Vosges)

Université de Bourgogne

UFR des Sciences de Santé

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# SERMENT D'HIPPOCRATE

*"Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.*

*Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.*

*Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.*

*J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.*

*Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.*

*J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.*

*Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.*

*Je donnerai mes soins à l'indigent et à quiconque me les demandera.*

*Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.*

*Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.*

*Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.*

*Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.*

*J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.*

*Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque."*

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**Aux membres du jury :**

**- Monsieur le Professeur Alexandre COCHET**
Professeur des universités - praticien hospitalier
Chef du service de spectroscopie RMN et médecine nucléaire
Vous me faîtes l'honneur d'être à la fois le président et directeur de cette thèse, acceptez mes sincères remerciements pour votre disponibilité, la qualité de votre encadrement, l'étendue de vos connaissances, vos relectures et suggestions dans ce travail.

**- Monsieur le Professeur Romaric LOFFROY**
Professeur des universités - praticien hospitalier
Chef du service radiologie et imagerie médicale diagnostique et thérapeutique
Mes remerciements pour votre participation à ce jury, pour le partage de vos connaissances et techniques sur l'ensemble de ma formation.

- **Monsieur le Docteur Paul-Mickaël WALKER**
Maître de conférences des universités - Praticien hospitalier – Biophysicien
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**-Monsieur le Docteur Aurélien LAMBERT**
Radiologue IM2P
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**À ma famille, mes amis et notamment :**

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À mon filleul Louis, bientôt grand frère.

À mes amis d'enfance, du lycée, de la faculté de Nancy, du CHU de Dijon, à notre quatuor derandonnée, dédicace à Baptiste pour son aide linguistique.

# TABLE DES MATIERES

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# Liste des abréviations

PSA : Prostatic Specific Antigen

BF : Biochemical Failure

BMI : Body Mass Index

PC : Prostate Cancer

RP : Radical Prostatectomy

mpMRI : multi-parametric Magnetic Resonance Imaging

DRE : Digital Rectal Examination

ISUP : International Society of Urological Pathology

AFMS : Anterior Fibromuscular Stroma

DCE : Dynamic Constrast Enhanced

ECE : Extra Capsular Extension

Pi-RADS : Prostate imaging-Reporting and Data System

AUC : Area Under Curve

**FACTEURS PRÉDICTIFS PRÉ-OPÉRATOIRES DE L'ÉCHEC BIOLOGIQUE PRÉCOCE DANS LE CANCER DE LA PROSTATE LOCALISÉ APRÈS PROSTATECTOMIE RADICALE**

**PREOPERATIVE PREDICTIVE FACTORS OF EARLY BIOCHEMICAL FAILURE IN LOCALIZED PROSTATE CANCER AFTER RADICAL PROSTATECTOMY**

## 1. Introduction

Avec plus de 55 000 cas et 9 000 décès par an en France le cancer de la prostate est le plus fréquent des cancers masculins (25 % des cas) [1]. L'âge moyen au diagnostic est d'environ 70 ans [1]. Depuis les années 1990, on observe une baisse de la mortalité grâceà une détection plus précoce et aux avancées thérapeutiques [2]. Le dépistage est individuel (toucher rectal et taux de PSA) mais reste controversé [3-4] car il peut conduire à un surdiagnostic et donc un surtraitement [2].

La prise en charge de référence du cancer de la prostate localisé repose sur lachirurgie, la radiothérapie externe ou la curiethérapie. La surveillance active [5] et de nouvelles thérapies sont également possibles (embolisation, cryothérapie, HIFU, radiofréquence) mais la plupart de ces techniques sont encore en cours d'évaluation [6].

La prostatectomie radicale (PR) reste le traitement le plus couramment utilisé pour les patients ayant une espérance de vie > 10 ans [6]. La récidive biologique à 10 ans va jusqu'à 40% selon les séries (avec un taux de mortalité associé de 6%) [7]. De plus, des complications spécifiques sont associée à la PR (incontinence, dysfonction érectile) [8]. Pour ces raisons, la sélection des patients avant chirurgie est essentielle. Le pronostic est actuellement orienté par des données cliniques et biologiques via les classifications de D'Amico ou NCCN (National Comprehensive Cancer Network) qui associent l'agressivité histologique (score de Gleason), l'extension anatomique (via le toucher rectal ou l'IRM) et le taux de PSA [6]. D'autres critères tels que l'indice de masse corporelle (IMC) [9] ou la densité du PSA [10] ont été décrits.

L'IRM multiparamétrique (IRMmp) (à 1,5 ou idéalement 3 Tesla pour la prostate) [11] est désormais couramment utilisée à visée de détection (critères PiRADS 2.1) [12], pourorienter la décision thérapeutique et à la recherche d'une récidive locale après traitement curatif [13 - 15].

Plusieurs facteurs prédictifs de récidive à l'IRM sont déjà connus comme par exemple l'analyse quantitative de l'ADC (association avec les cancers significatifs [16 - 19], avec l'agressivité tumorale (corrélation avec le score de Gleason et D'Amico) [20] et à la récidive [21], en particulier pour les patients à haut risque [22]). D'autres données IRM comme l'extension extra-prostatique, l'invasion des vésicules séminales, la taille de la lésion principale ou la localisation apicale (avant radiothérapie) sont également associées au risque de récidive [23]. Les séquences de perfusion en IRM fournissent également des informations utiles pour la détection et la caractérisation de la tumeur [24]. L'ensemble de ces données IRM peut guider la prise en charge thérapeutique en complément du score Pi-RADS [25].

À la suite d'une PR le taux de PSA doit être indétectable dans les 6 semaines [25]. La persistance d'un taux mesurable est considéré comme un échec biologique précoce, en lien avec des micro-métastases ou une maladie résiduelle. Une vélocité élevée du PSA et des caractéristiques anatomo-pathologiques défavorables tendent à indiquer une maladie métastatique [26]. Il n'existe néanmoins pas de consensus à ce sujet et la majorité des patients sont traités par radiothérapie de rattrapage seule [6]. Le taux de survie sans récidive néoplasique à 5 ans est faible (22%) mais la survie reste élevée (95% à 5 ans) [6].

Les facteurs prédictifs d'un échec biologique précoce sont peu décrits dans la littérature mais restent à priori proches de ceux de la récidive à distance : ils regroupent des données pré-opératoires (score de Gleason, stade T, IMC) et anatomo-pathologiques (stade T post-opératoire, extension extra-prostatique, positivité ganglionnaire, marge chirurgicale positive et volume tumoral) [27 - 28]. Cependant, il existe peu d'études sur les

facteurs prédictifs IRM.

L'objectif de notre étude était d'évaluer les facteurs prédictifs pré-opératoires d'une récidive biologique précoce après prostatectomie radicale dans le cancer de la prostate localisé en incluant des facteurs cliniques, biologiques, biopsiques et IRM.

With over 55,000 cases and 9,000 deaths each year in France, prostate cancer (PC) is the most common cancer in men (25% of all diagnosed) [1]. Average age at diagnosis is around 70 years [1]. Since the 90s there is a mortality decline thanks to earlier detection and therapeutic developments [2]. Screening is individual (digital rectal exam (DRE) and prostatic specific antigen (PSA) level) but remains controversial [3-4] because it can lead to overdiagnosis and overtreatment [2].

The standard care of localized prostate cancer relies on surgery, external radiotherapy or brachytherapy. Active surveillance [5] and new therapies are also possible (embolization, cryotherapy, HIFU, radio-frequency) but most of these techniques are still under evaluation [6].

Radical prostatectomy (RP) remains the most common treatment for patients with life expectancy > 10 years [6]. However, biochemical recurrence at 10 years following RP goes up to 40% (with an associated mortality rate of 6%) [7], and RP can have specific complications (incontinence, erectile dysfunction) [8]. For these reasons, selection of patients before RP appears essential. This selection is based on prognosis stratification, currently guided by clinical and biochemical data through D'Amico or NCCN (National Comprehensive Cancer Network) risk classifications, combining histological aggressiveness (ISUP grade / Gleason score), anatomical extension (with DRE or MRI) and PSA level [6]. Others criteria such as Body Mass Index (BMI) [9] or PSA density [10] have been described.

Multi-parametric Magnetic Resonance Imaging (mpMRI) of the prostate is now widely used in order to optimize cancer detection (PiRADS 2.1 standardized criteria) [11 -12], but

also for therapeutic decision guidance and research of local recurrence after curative treatment [13 - 15]. Several MRI prognostic factors are already related with cancer recurrence such as the quantitative analysis of ADC value (associated to significant cancer risk [16 - 19], tumor aggressiveness [20] and recurrence [21], especially for high-riskpatients [22]). Some others MRI data as extra-prostatic extension, invasion of seminal vesicles, size of the lesion or apical location (before radiotherapy) are also associated with risk of recurrence [23]. Dynamic acquisition also provides useful information for tumor detection and characterization [24]. All of these MRI data can guide the therapeuticmanagement in addition to the Pi-RADS score [25].

Plasmatic PSA level is expected to be undetectable within 6 weeks after successful RP [25]. Persistently measurable PSA in patients treated with RP is considered as an early BF and since it is thought to be due to residual cancer (either micrometastases or residual disease in the prostatic fossa). High PSA velocity and unfavorable pathological characteristics tend to point to metastatic disease [26]. Nevertheless, no consensus exists and the majority of patients are treated by salvage radiotherapy alone [6]. The recurrence-free survival rate at 5 years is low at 22% but survival in these patients group remains high (95% at 5 years) [6].

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, BMI) and pathologic criteria (post-operative stage, extra-prostatic extension, lymph node positivity, positive surgical margin and tumor volume) [27 - 28]. 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 for treatment of localized prostate cancer including clinical, biological, pathological and mpMRI factors.

## 2. Material and Methods

### 2.a Selection of patients

Between December 2012 and June 2018, 756 patients underwent RP in our institution for initial treatment of localized newly diagnosed PC. For this study, we have retrospectively selected patients who had the following inclusion criteria:

- Prostate cancer histologically proven by transrectal ultrasound guided biopsy ; biopsies performed according to PSA level / clinical examination (DRE) / clinical history (12 systematic biopsies according to current recommendations, more or less a few targeted biopsies (1 to 3) depending on the DRE, ultrasound or MRI).
- Curative treatment by radical prostatectomy ± lymph node dissection [6] after a collegial decision. For patients with intermediate or high risk according to D'Amico, staging was performed using CT and bone scintigraphy [6].
- A 3T multiparametric MRI performed in our institution before surgery (pre-therapeutic MRI).

Patients were excluded if they had one of the following criteria :

- Gleason score <6 on the pathological surgery report.
- A history of PC or any prostate surgery.
- Any cancer treatment before prostatectomy (including hormone therapy or radiotherapy).
- Evidence of lymph node involvement or distant metastasis on initial assessment.
- An initially uncontrolled disease (PSA level detectable despite adjuvant radiotherapy ± hormone therapy) which reflected a probable non-localized disease (micro-metastasis stage before surgery)

- Poor mpMRI quality (T1 hypersignal due to prostate bleeding, metal artifacts mainly related to total hip prosthesis, patient movement or digestive gas, incomplete MRI).
- MRI performed in another imaging center.

Thus, a total of 142 patients were included in this study. The local institutional review board approved this retrospective study and the requirement for informed consent was waived.

**2.b MRI technique and data**

All patients underwent MRI on a 3 Tesla magnet (Trio Tim, Siemens Healthcare) with a pelvic antenna [29]. The ideal time interval between biopsy and MRI was 6 to 8 weeks.**Table 1** summarizes the MRI protocol for imaging the prostate gland.
All MR images were archived using a PACS system (GE Healthcare).

**2.c MRI data analysis**

Data analysis was performed using the Image J software. All MR images were retrospectively reviewed by a trained radiologist who was not blinded from the initial report. We used Pi-RADS 2.0 version to classify lesions. An example of an MRI tumour lesion is attached in **Figure 1**.

The following global prostate data were assessed: prostate volume, the ADC value in healthy prostate (central and peripheral zone), the topography and the number of significant lesions (PIRADS score ≥ 3) and wash-in calculation (directing coefficient of the ascending slope) from DCE - MRI in healthy prostate (central zone and peripheral zone).
If more than one intraprostatic lesion was present, the index (dominant) lesion was defined as the one with the highest PIRADS score, and the largest diameter.

For the evaluation of the index lesion, the following data were assessed: diameter (on axial T2 sequence), location (central or peripheral gland), presence of a capsular contact (measured along the perimeter of the prostate to avoid a linear distance), tumor wash-in, tumor perfusion curve from 1 to 3, ADC value (average ROI including the whole lesion and calculated average of the 10% of the lowest values). Finally, MRI T stage was defined.
To estimate presence of a T3a stage (extra-capsular extension (ECE)) reader used in agreement with the MRI report the five-point Likert scale (1 : definitely absent / 2 : probably absent / 3 : equivocal / 4 : probably present / 5 : definitely present). The ECE was doubtful from 3. Standard criteria from European Society of Urogenital Radiology (ESUR) [30] included irregularity or neurovascular bundle thickening, bulge or loss of capsule and capsular enhancement, measurable extra-capsular disease and obliteration of the recto-prostatic angle.

**2.d Clinical, biological and pathological data**

Data and medical history of each patient were extracted using DxCare software (computerized data since 2008 in our center). All pathological data were analyzed in our pathology department. PSA plasma level measurement was not necessarily performed in our institution.

Computed clinical and pathological data were :

- Age at diagnosis (date of biopsies result).
- Time interval between diagnosis and surgery and between MRI and surgery.
- Clinical T stage (based on 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) following surgery.
- 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 for NCCN

categorization.

- 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 / extra-capsular extension (not invaded - invaded not exceeded - invaded exceeded) / invasion of seminal vesicles / surgical margin (R0 - R1 - R2).

For each patient, follow-up data were: annual PSA level, date of recurrence, survival status (prostate cancer death if applicable) and effective follow-up duration in months (and rate of follow- up ≥ 5 years).

From clinical, biological, pathological and MRI data, other elements have been extrapolated:

- For each cancer described on pathological report: concordance with MRI status and topography of concordance with positives biopsies.
- staging of each patient according to NCCN classification. Three variants of this score were determined: the common clinical version (including PSA level, clinical stage based on DRE and biopsy Gleason score), the MRI version (MRI stage instead of clinical stage) and the pathological version (stage and Gleason of the prostatectomy pathological report). We didn't use D'Amico's classification because of the absence of the Gleason 7 dichotomy (3+4 versus 4+3). Indeed a Gleason threshold score of 4+3 is associated with significant cancer [31].

**2.e Follow-up data**

Regular follow-up by measurement PSA level and consultation with an urologist from our center (every year at least) was scheduled. Otherwise the patient was followed 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.

**2.f Statistical analysis**

Qualitative data were described using number (percentage) and quantitative data using median and interquartile (range). Patient were categorized according to absence or presence of early biochemical failure (BF), defined as a PSA level > 0.10 ng/ml 6 weeks after surgery, confirmed at 3 months after surgery [32] if initially dubious (in order to eliminate persistence of healthy prostate tissue). For continuous variables, comparisons between the two groups were performed using the Student t test or the Wilcoxon test depending on the normality of the distribution. The $\chi 2$ test or the Fisher exact test was used for categorical variables.

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. Three different bivariate models were created by combination of these variables. Odds ratio 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.

## 3) Results

### 3.a Characteristics of patients.

Clinical and biological characteristics of patients before treatment are reported in **Table 2**.

Median diagnosis age was 65 years [61 - 68]. The median time interval between diagnosis and surgery was 3.5 months [2.4 - 4.4]. The most common stage of DRE was T1c (51%). The topographical concordance of the biopsies with pathological data was 86% (103 patients - 84 % in no early BF group versus 19 patients (95%) in early BF group - p = 0.31). Patients with early BF had higher PSA level before surgery, higher Gleason score according to biopsies (p<0.0001 for both), higher number of positive biopsies and tumor biopsy core length (p=0.0008 and 0.0005 respectively), and higher NCCN risk classification (p=0.0003). In contrast, there was no difference among the groups concerning age, time interval between diagnosis and surgery, and clinical T stage.

### 3.b Preoperative MRI

Preoperative MRI data are reported in **Table 3 and 4**.

Most of the patients (109 – 77 %) had diagnostic biopsies before MRI. The MRI interpretation has been hampered in 49 patients (35%) most of the time by hemorrhagic artefacts (37 - 76 %). 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 – (p=0.13). 10 (7 %) of the 142 patients didn't have target lesion visible on MRI. None of them were in the significant post-operative PSA level group. There was no difference among the groups concerning all these parameters. Giving their low numbers, targets in anterior fibromuscular stroma (AFMS) were then analyzed with central zone targets. MRI T stage and MRI NCCN risk classification were significantly different among the groups

(p<0.0001). 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 (5%) in the other group.

There were 157 target lesions identified for the 132 patients with at least one MRI target lesion. (thus 10 patients with a MRI T1c stage). The main MRI lesion was the most often localized in the peripheral zone (97 out of 132 patients - 74%)). A Pi-RADS 5 score was most frequently found in both groups (78 patients - 59 %). Most of the target lesions had a capsular contact (123 - 93 %). The prevalence of these criteria weren't different between our two groups. There were 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=0.013). The DCE-MRI study with wash-in coefficient (p=0.093) or perfusion curves (p=0.966) were also insignificant.

Only two MRI target lesion factors were significant : the length of the capsular contact and the tumor size (p<0.0001 for both).

**3.c Postoperative pathological data**

Postoperative pathological data are reported in **Table 5**.

There were 254 tumor lesion in our 142 patients, many of MRI unseen foci were sub-centimetric 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 criteria. Patients with early BF more frequently had lymph node involvement (p<0.0001 - 11 out of 20 early BF with proven lymph node involvement).
As with the pre-operative data, Gleason score / T stage / NCCN risk classification and the size of the main tumor focus also showed significant differences among the groups(p<0.0001).
Pathological extra-capsular extension, surgical margin (R1) and seminal vesicle invasion were also significantly different (p<0.0001). Indeed 12 out of the 20 patients in group 2 (60%) had

a seminal vesicle invasion versus 9 (7%) out of the 122 patients without early BF.

**3.d Post-operative data and follow-up**

Following surgery, 33 patients (23%) received adjuvant treatment including all patients in the post-operative PSA group and 14 patients in no early BF group (12%) . These patients received radiotherapy (12 - 36 %), hormone therapy (2 - 6 %) or both treatments (19 - 58% including 15 patients (79%) in early BF group) after a collegial decision. One patient rejected hormone therapy following radiotherapy (in no early BF group). In the early BF group, the median PSA level 6 weeks after surgery was 0.48 ng/ml [0.19 - 1.21].

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

**3.e Predictive factors of early BF**

Logistic regression analysis was performed to determine predictive factors of early BF. All parameters listed in Table 2, 3 and 4 were tested by univariate analysis. **Table 6** report significant (p<0.01) univariate predictors of early BF.

Pre-surgery PSA level (threshold of 10 or 20 ng/ml as used in NCCN classification) didn't show any association with early BF. Analysis of the Gleason score with ISUP grades showed an association from 4+3 score (p=0.0009). 32 patients (22 %) had a threshold ≥ 4+3 of which 13 (41 %) had early BF (OR 9.6 [2.5 - 36.8] - p<0.0001). For other biopsy criteria, having at least 4 positive biopsies were not significant but having a largest positive biopsy (cancer core lenght) at least at 7mm was associated with early BF (OR 4.3 [1.1 - 17.1] -

p=0.006). The clinical NCCN risk classification was also significant: at least an "unfavourable intermediate" group was associated with early BF (OR 6.0 [1.4- 26.0] - p=0.0015).

For MRI analysis the best parameter to predict early BF was T3a stage. Indeed having a T3 or T4 stage was strongly associated with early BF (17 out of 39 patients - OR 22,3 [4.4 - 114.5]- p<0.0001) more than a threshold at T2c (OR 13.0 [1.4 - 123.2]- p=0.003).
The main target size wasn't significant for a cut off chosen at 17 mm.
Concerning capsular contact length we took two cut offs : 10mm (commonly used in relation to ESUR recommendations [30]) which wasn't significant here (OR = 3.0 [0.9 - 9.1]- p=0.06) but the cut off at 20 mm [33] was significant (OR = 8.7 [2.1 - 36.3]- p<0.001).
The MRI NCCN classification was also relevant for patients with high or very high risk (OR 13.9 - p<0.0001).

For multivariate analysis, the following parameters were associated two by two:
- pre-operative criteria : Gleason biopsy score, biopsy core length (threshold at 7mm) and NCCN classification (threshold at intermediate unfavorable risk).
- MRI criteria : T stage≥3, NCCN MRI risk (> high risk), capsular contact > 20mm for index lesion .

We tested pairwise combinations of only pre-operative, only MRI or mixed data. Only relevant analyses are reported in Table 7 (p<0.01 and AUC(99%) ≥ 0.80). The best association for prediction of early BF was preoperative Gleason score ≥4+3 and MRI T stage ≥3 **(Figure 2).** 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%.

## 4. Discussion

RP remains the treatment of choice for eradication of localized PC. Nerve-sparing RP can be performed safely in a majority of men in order to preserve parasympathetic nerve branches of the pelvis plexus and then spare erectile function [34]. However, 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 that have recently been updated by Mottet N and al [35]. It has been recognized that mpMRI may be helpful for selecting a nerve-sparing approach because it has good specificity but low sensitivity for detecting pT3a stages. However, given the high incidence of PC and the high cost of MRI, the role of MRI in initial staging of PC is still under debate. Previous studies have shown the interest of mpMRI for prediction of recurrence following RP [20-23 and 36-37]. By focusing on prediction of persistence of detectable post-operative PSA, defined in our study as early biochemical failure, our result emphasize the crucial role of mpMRI before RP.

Gleason score on biopsies, MRI capsular contact length and MRI T stage confirm their major role in post-operative PSA significant level prediction. Neither the association of pre-operative data (excluding MRI) nor the association of MRI data only is relevant whereas the combination of these two categories is significant.

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 >20mm), all with negative predictive values >90%. A multivariate prognostic score combining these different factors should be refined by a larger cohort to predict the effectiveness of surgery especially since patients with early BF have a high risk of recurrence.

The distribution of index lesions didn’t show any topographical predominance outside the usual distribution of cancers between peripheral zone (about 70%) and central zone

(about 30%) [6] In contrast to other studies on the subject [38]. The number of target lesionson MRI didn't influence the risk of early BF. The patient's prognosis is largely driven by the characteristics of the index lesion in the case of a radical prostatectomy. Nevertheless this data could be interesting to study in partial surgeries or in focal treatments versus radical

prostatectomy.

MRI T-stage is logically a major factor of association with early BF, comparable to pathological T-stage ($p<0.0001$ for both). T3 or higher suspected T-stage on MRI is the best threshold to predict early PSA failure [39] despite the relative subjectivity of extra-capsular extension on MRI. MRI T stage brings an overestimation of NCCN MRI classification compared to standard NCCN version [40]. Sixteen (80%) of the 20 patients in Group 2 have

an MRI stage ≥ T3a and 17 (85%) have an MRI NCCN stage ≥ high risk.

Many pathological tumor lesions were not visualized on MRI, according to the sub- centimetric size of most unseen tumor foci (often non-significant cancers with Gleason Scoreat 6) and by the conditions under which the examinations were performed (hemorrhagic artifacts post-biopsy). As in other studies on recurrence factors, the size of the target lesion is also associated with the risk of post-operative PSA but Pi-RADS score is not significant in our study contrary to data about recurrence [41] and the detection of a significant cancer

[42].

Our data shows a limit of significance of the target/healthy area ADC ratio which is

potentially explained by the size of our cohort (20 patients in group 2), the interest of ADC value in detecting significant lesions and the estimation of the aggressiveness having already been demonstrated [23, 43]. 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. However, the role of quantitative perfusion in the prediction of significant lesion/

tumor aggressiveness have already been demonstrated [24 - 44 - 45].

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 10mm threshold and 20mm according to the recent study by Gustavo Mendez et al [33]. A threshold of 20 mm seems more relevant than 10mm to predict an early BF (50% of patients in group 2 for 20mm). According to our results, it is clear that mpMRI improves the tumor T classification and modifies the prognostic of prostate cancer even if it remains dependent and limited bythe radiologist's experience and the variability of interpretation for subjective imaging elements.

Our study has several limitations. The sample size, as well as the retrospective natureof this single institution study, limits the generalizability of our results. The majority of the biopsies weren't directed by a prior MRI. Many MRI interpretations were limited by hemorrhagic artifacts. 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 [46]. Our MRI detection sensitivity could have been reduced because of these conditions.

## 5. Conclusion

Combination of preoperative Gleason score and T stage based on mpMRI permits to predict persistence of detectable PSA (early BF) following radical prostatectomy for patients with localized PC, with a high accuracy (positive and negative predictive value of 75 and 94% respectively).

These results highlights the major importance of mpMRI in the initial staging of PC,for lesion detection but also for prognostic stratification, in order to optimize therapeutic strategies.

**THESE SOUTENUE PAR MONSIEUR JEREMY CASSIN**

**CONCLUSIONS**

La prédiction de l'échec biologique précoce après une prostatectomie radicale dans le cancer de la prostate inclut des facteurs biologiques (niveau de PSA), biopsiques (score de Gleason, nombre de biopsies positives, longueur de l'atteinte tumorale) et IRM (stade T, largeur du contact capsulaire, ganglion péri-prostatique). Ces données sont logiquement proches de celles de la récidive à distance. Un score pronostique global avec ces différents critères est à envisager pour prédire le risque d'une chirurgie inefficace et aider à la décision thérapeutique.

Le Président du jury,

Pr. A. COCHET

Vu et permis d'imprimer
Dijon, le 15 MARS 2021
Le Doyen

Pr. M. MAYNADIÉ

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# ANNEXES

**Table 1 :** MRI protocol

| Parameter | T2-Weighted Imaging | DWI | DCE - MRI (T1 VIBE FAT SAT) |
|---|---|---|---|
| Orientation | 3 planes | Axial | Axial |
| TR (ms) | 3600 | 4200 | 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 |

DCE-MRI : Dynamic contrat enhanced MRI / NA : not applicable / injection of gadolinium 1,4,7,10- tetrazacyclododecane-1,4,7,10-tetraacetic acid (Dotarem, Guerbet, France) at a dose of 0.1 mmol/kg using a power injector, followed by a 20 mL saline flush.
Apparent Diffusion Coefficient maps were generated with b values of 100 and 800 s/mm$^2$

**Table 2** : **Preoperative clinical and biological characteristics of patients.** Results are expressed as number (percentage) for categorical variables and median [interquartile range] for continuous variables. BF= Biochemical failure.

| Parameter | All patients (n=142) | No early BF (n=122) | Early BF (n=20) | P value |
|---|---|---|---|---|
| **Age (year)** | 65 [61 - 68] | 64 [60 - 67] | 66 [63 - 69] | 0.213 |
| **PSA (ng/ml)** | 7.3 [5.6 - 9.6] | 7.1 [5.5 - 9.0] | 9.3 [7.4 - 14.5] | **<.0001** |
| **Clinical T stage** | | | | |
| T1c | 73 | 66 | 7 | 0.236 |
| 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 - 4.0] | 0.186 |
| **Gleason score** | | | | |
| **3+3** | 63 | 60 | 3 | **<.0001** |
| **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] | **0.0008** |
| **Biopsy core length (mm)** | 7.0 [4.0 - 10.0] | 6.5 [4.0 - 10.0] | 10.5 [7.5 - 13.5] | **0.0005** |
| **Clinical NCCN risk classification** | | | | |
| - (Very) low | 40 | 38 | 2 | **0.0003** |
| - Intermediate Favorable | 40 | 38 | 2 | |
| - Intermediate Unfavorable | 42 | 32 | 10 | |
| - (Very) High | 20 | 14 | 6 | |

**Table 3 : Preoperative MRI parameters (global characteristics).** Results are expressed asnumber (percentage) for categorical variables and median [interquartile range] for continuous variables.

| Parameter | All patients (n=142) | No early BF (n=122) | Early BF (n=20) | P value |
|---|---|---|---|---|
| **Time interval between MRI and surgery** | 2.6 [1.4 - 4.1] | 2.6 [1.4 - 4.1] | 2.6 [1.3 - 4.3] | 0.858 |
| **MRI performed before biopsies** | 33 (23.2%) | 25 (20.5%) | 8 (40.0%) | 0.079 |
| **Prostatic volume** | 45 [35 - 62] | 43 [34 - 61] | 55 [46 - 66] | 0.048 |
| **PSA density** | 0.13 [0.10 - 0.18] | 0.13 [0.09 - 0.17] | 0.16 [0.12 - 0.27] | 0.055 |
| **Number of lesions** | | | | |
| 0 | 10 | 10 | 0 | |
| 1 | 106 | 92 | 14 | 0.262 |
| 2 | 22 | 17 | 5 | |
| 3 | 4 | 3 | 1 | |
| **MRI T stage** | | | | |
| T2a | 44 | 43 | 1 | |
| T2b | 8 | 8 | 0 | |
| T2c | 42 | 39 | 3 | **<.0001** |
| T3a | 22 | 16 | 6 | |
| T3b | 15 | 5 | 10 | |
| T4 | 1 | 1 | 0 | |
| **MRI NCCN risk classification** | | | | |
| - (Very) Low | 28 | 28 | 0 | |
| - Intermediate favorable | 23 | 22 | 1 | **<.0001** |
| - Intermediate unfavorable | 42 | 40 | 2 | |
| - (Very) High | 49 | 32 | 17 | |

**Table 4: Preoperative MRI data (index lesion characteristics).** Results are expressed as number (percentage) for categorical variables and median [interquartile range] for continuous variables.

| Parameter | All patients (n=132) | No early BF (n=112) | Early BF (n=20) | P value |
|---|---|---|---|---|
| **PIRADS V 2.0** | | | | |
| **3** | 4 | 4 | 0 | 0.032 |
| **4** | 50 | 47 | 3 | |
| **5** | 78 | 61 | 17 | |
| **Tumor location** | | | | |
| **- Peripheral Zone** | 97 | 79 | 18 | 0.237 |
| **- Central Zone** | 32 | 30 | 2 | |
| **- AFMS** | 3 | 3 | 0 | |
| **Tumor size (mm)** | 16 [12 - 21] | 15 [11 - 21] | 20 [14 - 37] | **<.0001** |
| **Capsular contact (yes)** | 123 (93.2%) | 103 (92.0%) | 20 (100.0%) | 0.354 |
| **Length of capsular contact (mm)** | 13 [9 - 18] | 12 [9 - 16] | 21 [15 - 38] | **<.0001** |
| **ADC value ($mm^2/s$)** | 808 [701 - 933] | 826 [713 - 936] | 760 [636 - 860] | 0.060 |
| **Average of the lowest 10% of ADC value ($mm^2/s$)** | 591 [453 - 742] | 602 [468 - 747] | 566 [409 - 679] | 0.217 |
| **Ratio ADC lesion / ADC healthy area** | 0.5 [0.4 - 0.6] | 0.6 [0.5 - 0.6] | 0.5 [0.4 - 0.6] | 0.013 |
| **Wash in coefficient** | 200 [156 - 267] | 197 [152 - 259] | 222[190 - 272] | 0.093 |
| **Type of perfusion curve** | | | | |
| 1 | 6 | 5 | 1 | 0.966 |
| 2 | 43 | 36 | 7 | |
| 3 | 83 | 71 | 12 | |

**Table 5: Postoperative pathological data.** Results are expressed as number (percentage) for categorical variables and median [interquartile range] for continuous variables.

| Parameter | All patients (n=142) | No early BF (n=122) | Early BF (n=20) | P value |
|---|---|---|---|---|
| **Prostate weight (g)** | 55 [46 - 71] | 54 [46 - 70] | 57 [52 - 80] | 0.099 |
| **Number of lesions** | | | | |
| 1 | 57 | 49 | 8 | |
| 2 | 59 | 52 | 7 | 0.230 |
| 3 | 25 | 21 | 4 | |
| 4 | 1 | 0 | 1 | |
| **Gleason score** | | | | |
| 3+3 | 20 | 19 | 1 | |
| 3+4 | 81 | 78 | 3 | **<.0001** |
| 4+3 | 21 | 13 | 8 | |
| 4+4 | 13 | 8 | 5 | |
| >4+4 | 7 | 4 | 3 | |
| **Pathological T stage** | | | | |
| T2a | 17 | 17 | 0 | |
| T2b | 1 | 1 | 0 | |
| T2c | 67 | 64 | 3 | **<.0001** |
| T3a | 36 | 31 | 5 | |
| T3b | 20 | 9 | 11 | |
| T4 | 1 | 0 | 1 | |
| **Pathological NCCN classification** | | | | |
| - (Very) low | 4 | 4 | 0 | |
| - Intermediate favorable | 19 | 18 | 1 | **<.0001** |
| Intermediate unfavorable | 55 | 53 | 2 | |
| (Very) high | 64 | 47 | 17 | |
| **Lymph node dissection** | 60 (42.3%) | 44 (36.1%) | 16 (80.0%) | **0.0002** |
| **Lymph node invasion (n=60)** | 13 (21.7%) | 2 (4.5%) | 11 (68.8%) | **<.0001** |
| **Size of the index lesion (mm)** | 22 [16 - 28] | 20 [16 - 26] | 35 [28 - 46] | **<.0001** |
| **Extra-capsular extension** | | | | |
| Not invaded | 39 | 39 | 0 | |
| Invaded not exceeded | 48 | 45 | 3 | **<.0001** |
| Invaded exceeded | 55 | 38 | 17 | |
| **Invasion of seminal vesicles** | 21 (14.8%) | 9 (7.4%) | 12 (60.0%) | **<.0001** |
| **Margins** | | | | |
| **R0** | 104 | 97 | 7 | **<.0001** |
| **R1** | 38 | 25 | 13 | |

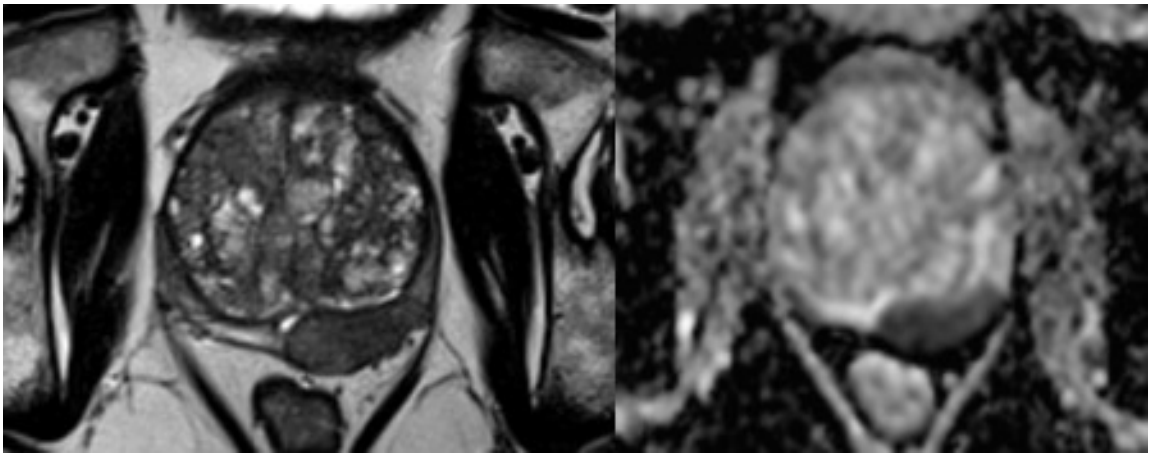
**Table 6 : univariate predictors of early BF.**

| | OR | 99% CI | P value | AUC |
|---|---|---|---|---|
| **Gleason score ≥4+3** | 9.6 | [2.5 - 36.8] | <.0001 | 0.75 |
| **Tumor biopsy core length > 7mm** | 4.3 | [1.1 - 17.1] | 0.006 | 0.71 |
| **Clinical NCCN classification ≥ intermediate unfavorable** | 6.0 | [1.4- 26.0] | 0.0015 | 0.71 |
| **MRI NCCN risk classification ≥ high risk** | 13.9 | [2.8 - 69.5] | <.0001 | 0.79 |
| **MRI T stage ≥ 3** | 22.3 | [4.4 - 114.5] | <.0001 | 0.83 |
| **Size of capsular contact > 20 mm** | 8.7 | [2.1 - 36.3] | <.0001 | 0.70 |

**Table 7 : multivariate predictors of early BF**

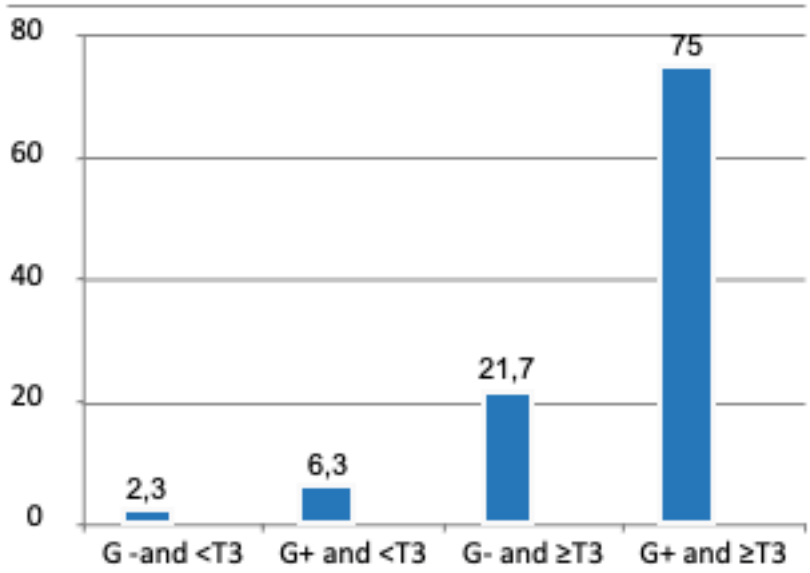
| | OR (99% CI) | p value | AUC (99% CI) |
|---|---|---|---|
| **Model 1** | | | AUC [CI99%] = 0.80 [0.64 - 0.95] |
| **Gleason ≥4+3** | 6.6 [1.6 - 28.3] | 0.0008 | |
| **Capsular contact length > 20mm** | 6.3 [1.3 - 29.7] | 0.0024 | |
| **Model 2** | | | AUC [CI99%] = 0.89 [0.77 - 1.00] |
| **Gleason ≥4+3** | 6.8 [1.4 - 32.5] | 0.0015 | |
| **MRI T Stage ≥ 3** | 17,4 [3.2 - 94.9] | < 0.0001 | |
| **Model 3** | | 0,0012 | AUC [CI99%] = 0.83 [0.69 - 0.96] |
| **NCCN IRM ≥ high risk** | 8.1 [2.2 - 106.3] | | |
| **Capsular contact length > 20mm** | 4.82 [1.1 - 22.7] | 0.0089 | |

**FIGURE 1: Example of ZP target lesion**



A 63-year-old man with an abnormal DRE (T2b), PSA plasma level at 15.9 ng/mL and Gleason score 4+ 4. PC in 7 of 14 cores on transrectal ultrasound-guided biopsy. Axial T2-weighed MR image showeda PiRADS 5 lesion, measured tumor capsular contact length was 34 mm and MRI extracapsular extension has been described then confirmed after surgery.

**FIGURE 2: incidence (%) of early BF according to absence or presence of Gleason score ≥4+3 and MRI T stage ≥3.**




G-: Gleason score <4+3 / G+: Gleason score ≥ 4+3 (on biopsies).

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

**TITRE DE LA THESE :** Facteurs prédictifs pré-opératoires de l'échec biologique précoce dans le cancer de la prostatelocalisé après prostatectomie radicale.

Preoperative predictive factors of early biochemical failure in localized prostate cancer after radicalprostatectomy.

**AUTEUR : JEREMY CASSIN**

**RESUME :**

CONTEXTE : L'objectif de notre étude était d'évaluer les facteurs prédictifs (cliniques biologiques etIRM) d'un échec biologique précoce après une prostatectomie radicale dans un cancer de la prostate localisé.

MÉTHODES : Nous avons inclus rétrospectivement 142 patients de notre centre hospitalier universitaire ayant bénéficié d'une IRM à 3 Tesla avant une prostatectomie radicale. Tous les cancers de la prostate ont été confirmés par biopsie, toutes les interventions chirurgicales ont été validées enréunion pluri-disciplinaire pour une maladie localisée. Seules les lésions cibles de l'IRM (PiRADS ≥ 3) avec une correspondance histologique ont été considérées comme significatives. Des données cliniques, biologiques, IRM et anatomo-pathologiques ont été étudiées.

RÉSULTATS : Un échec biologique précoce est survenu chez 14% des patients (20/142). Ces patients avaient un taux de PSA plus élevé au diagnostic, un score de Gleason, un nombre de biopsiespositives et une taille de la plus grande biopsie positive plus élevés, ainsi qu'un score de risque NCCN plus élevé ($p<0,01$ pour tous). Selon l'IRM, ils présentaient également un stade T plus élevé et une taille de contact capsulaire plus importante ($p<0,001$ pour tous). En revanche, il n'y avait aucune différence concernant les valeurs d'ADC, l'imagerie de perfusion et la localisation de la lésion index.

En analyse multivariée, la meilleure combinaison de facteurs prédictifs d'un échec biologique précoce était l'association d'un score de Gleason pré-opératoire ≥4+3 (OR=6,8 [1,4-32,5], $p=0,0015$) et d'un stade T≥3 à l'IRM(OR=17,4 [3,2-94,9], $p<0,0001$) avec une aire sous la courbe de 0,89 [0,77-1], une valeur prédictive négative de 94% et une valeur prédictive positive de 75%.

CONCLUSION : La combinaison de marqueurs pré-opératoires simples comme le score de Gleason et le stade T IRM permet de stratifier avec précision le risque d'échec biologique précoce après une prostatectomie radicale. Ces résultats soulignent le rôle central de l'IRM pré-opératoire dans lagestion du cancer de la prostate localisé.

**MOTS-CLÉS :** Cancer de la prostate - Imagerie par résonance magnétique - Prostatectomie radicale - PSA post-opératoire.