Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

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N°

TITRE DE LA THESE

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THESE
Présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

et soutenue publiquement le 15/04/2021

pour obtenir le grade de Docteur en Médecine

par Audrey ASUNCION

Née le 16/10/1993

A Clermont-Ferrand

Université de Bourgogne

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"Au moment d'être admise 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.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue 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 déshonorée et méprisée si j'y manque."

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Aux membres de mon jury

A Monsieur le Professeur LOFFROY, président du jury :

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Vous me faites l'honneur d'avoir accepté de présider mon jury. Veuillez trouver l'expression de mes sincères sentiments et de mon profond respect.

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ADC: apparent diffusion coefficient

bRFS: biochemical relapse free survival

BT: brachytherapy

CGFL: Georges François Leclerc Center

Cho: choline

Cit: citrate

CZ: central zone

DCE: dynamic contrast enhanced

DRE: digital rectal examination

DWI: diffusion weighted images

EBRT: external beam radiotherapy

ECE: extra capsular effraction

HC: Harrell coefficient

HT: hormonotherapy

INCA: Institut National du CAncer

mpMRI: multiparametric Magnetic Resonance Imaging

MRI: Magnetic Resonance Imaging

MRSI: Magnetic Resonance Spectroscopic Imaging

NCCN: National Comprehensive Cancer Network

PI-RADS: Prostate Imaging Reporting and Data System

PSA: Prostate Specific Antigen

PZ: peripheral zone

SFMA: anterior fibromuscular stroma

TSE: turbo spin echo

TZ: transitional zone

UICC: International Union Against Cancer

3T: 3 Tesla

1.1 INTRODUCTION (français)

Le cancer de la prostate représente aujourd'hui 25 % des cancers masculins et, avec un dixième des décès par cancer, il est la deuxième cause de décès par cancer chez les hommes en Europe occidentale et aux États-Unis [1–2].

Le cancer de la prostate à un stade précoce est généralement traité par prostatectomie radicale, radiothérapie externe ou curiethérapie, tandis que les formes histologiques ou cliniques plus sévères, dont le pronostic est souvent moins bon, nécessitent des thérapies multimodales comprenant chirurgie et radiothérapie ou radiothérapie avec hormonothérapie adjuvante, celle-ci pouvant durer plusieurs années.

Le choix du traitement dépend largement du groupe à risque dans lequel est classé le patient. Ces groupes basés sur les travaux de d'Amico [3] et des recommandations du National Comprehensive Cancer Network (NCCN) [4] sont bien établis et largement utilisés aujourd'hui, basés sur le taux de PSA, le stade T clinique (défini par l'étude du toucher rectal et les résultats des biopsies) et le score de Gleason évalué sur les résultats anatomopathologiques.

Cependant, malgré une classification rigoureuse des patients en fonction de la gravité de leur maladie, et donc d'un choix d'un traitement approprié pour ces cancers localisés de prostate, plus de la moitié des patients connaîtront une récidive biochimique dans les 10 ans [5–6]. Ainsi, en raison de la faible sensibilité (33%) et de la grande variabilité inter-observateur du toucher rectal [7–8], l'IRM multiparamétrique joue un rôle de plus en plus important dans le diagnostic, notamment dans la détection de la localisation tumorale (83%) chez les patients dont le taux de PSA est élevé, mais dont les résultats des biopsies sont négatifs [9]. Par ailleurs, la littérature a montré son intérêt majeur dans l'établissement du stade tumoral [10–11], notamment dans la détection d'une atteinte extra capsulaire ou des vésicules séminales [12–13–14–15].

En 2012 et 2015, les algorithmes PI-RADS version 1 [16] et PI-RADS version 2 [17] ont été conçus par des experts en IRM prostatique afin de graduer le risque de malignité en standardisant l'interprétation des lésions visibles dans la zone transitionnelle et périphérique à l'aide d'une échelle en 5 points, moins subjective que l'échelle de Likert.

Aujourd'hui, l'utilisation de la classification PIRADS v2 en IRM, faite pour stratifier le risque, est de plus en plus fréquemment utilisée pour réajuster le stade T, en complément des

biopsies et du toucher rectal [18]. En effet, le Comité d'organisation de cette échelle PI-RADS a récemment recommandé plusieurs modifications du PI-RADS v2 annonçant la naissance d'une nouvelle version : PIRADS v2.1 [19].

Dans un autre registre, l'imagerie spectroscopique qui permet d'analyser le métabolisme de l'ensemble de la prostate, s'est révélée combinée à l'IRM 3T être un outil prometteur pour la détection tumorale [20]. Dans les travaux de Scheidler [21], l'ajout de l'imagerie spectroscopique a donné de meilleurs résultats que l'IRM seule quant à la localisation des sites cancéreux, avec une spécificité de 90 % et une sensibilité de 50 %. Par ailleurs, la spectroscopie a montré son intérêt dans l'évaluation de l'extension extra capsulaire, du volume tumoral sur l'IRM initiale [22] ou dans l'amélioration du rendement des biopsies [23]. D'autres études ont également mis en évidence l'intérêt de coupler IRM et spectroscopie pour détecter une maladie résiduelle ou une récidive locale par la persistance d'un profil métabolique, notamment chez les patients traités par radiothérapie externe [24–25].

Néanmoins, on ne sait pas encore si le stade T défini par l'IRM ou le PIRADS v2 peut mieux prédire le pronostic des patients traités par radiothérapie, en utilisant la classification des groupes à risque du NCCN. La valeur pronostique de l'IRM a été étudiée dans des séries après chirurgie où le score de Gleason et le stade T ont été établis sur la pièce de prostatectomie radicale [26].

Ainsi, après radiothérapie externe, peu d'études à notre connaissance ont pu établir des facteurs pronostiques de récidive sur l'IRM initiale, notamment concernant l'apport potentiel des données de spectroscopie.

C'est pourquoi nous avons entrepris cette étude afin d'évaluer si les résultats combinés de l'IRM pelvienne et des données spectroscopiques pré-thérapeutiques sont prédictifs de récidive biochimique chez les patients traités par radiothérapie externe ou curiethérapie pour cancer localisé de prostate.

1.2 INTRODUCTION

Prostate cancer now accounts for 25% of male cancers and with one tenth of cancer deaths, it is the second leading cause of cancer deaths in men in Western Europe and in the United States [1–2].

Early stage prostate cancer is usually treated by radical prostatectomy, external beam radiotherapy (EBRT) or brachytherapy (BT) whilst more severe histological or clinical forms, which often have poorer prognosis, require multimodal therapies such as surgery with radiotherapy or radiotherapy combined with hormone therapy that can last several years.

The choice of treatment depends largely on the risk group in which the patient is classified. Such risk groups, based on the work of d'Amico and colleagues [3] and the recommendations from the National Comprehensive Cancer Network (NCCN) [4] are well established and widely used today. These different risk groups are based on PSA level, clinical T-stage (defined by the digital rectal examination study and the biopsy results) and the Gleason score evaluated on the anatomopathological results.

However, despite a rigorous classification of patients according to the severity of their illness, and therefore the choice of appropriate treatment for localized prostate cancer, more than half of the patients will experience a biochemical recurrence within 10 years [5–6]. Thus, due to the low sensitivity (33%) and high inter-observer variability of the digital rectal examination (DRE) [7–8], multiparametric MRI (mpMRI) has been playing an increasingly important role in diagnosis, including the detection of tumor location (83%) for patients with PSA levels indicative of cancer, but with negative biopsy results [9]. Furthermore, the literature has shown its major interest in the establishment of the tumor stage [10–11], particularly in the detection of extra capsular or seminal vesicle damage [12–13–14–15].

In 2012 and 2015, the PI-RADS version 1[16] and PI-RADS version 2 [17] algorithms were designed by experts on prostate mpMRI in order to graduate the risk of malignancy by standardizing the interpretation of visible lesions in the transitional (TZ) and peripheral (PZ) zone using a 5-point scale, less subjective than the Likert scale.

Nowadays, the use of the PIRADS v2 classification in MRI, made to stratify the risk, is more and more frequently used to readjust the T-stage, as a complement to biopsies and DRE [18]. Indeed, the PI-RADS Steering Committee has recently recommended several modifications to PI-RADS v2 heralding the birth of a new version: PIRADS v2.1 [19].

On another register, MR spectroscopic imaging (MRSI) allows the analysis of metabolism in the entire prostate gland, and combined with MRI, it has shown some promise in the detection of cancer on 3T MRI [20]. In Scheidler's work [21] on tumor localization, the addition of MRSI fared better than MRI alone, with 90% specificity and 50% sensitivity. In addition, spectroscopy has shown its interest in the evaluation of extra capsular extension, tumor volume on initial MRI [22] or in the improvement of biopsy yield [23]. Other studies have also brought to light the benefit of coupling MRI and spectroscopy to detect residual disease or local recurrence by the persistence of a metabolic profile, especially for patients treated by external beam radiotherapy [24–25].

Nevertheless, whether T-stage defined on MRI or PIRADS v2 can better predict the prognostic of patients after radiotherapy, using the NCCN risk group classification remains uncertain. The prognostic value of mpMRI was studied in series after surgery where the Gleason score and T-stage were established on the radical prostatectomy piece [26].
Thus, after external beam radiotherapy, few studies to our knowledge have been able to establish prognostic factors for MRI recurrence, especially concerning the potential contribution of spectroscopy data.

Therefore, we undertook this study to evaluate whether pretreatment combined pelvic MRI and MRSI findings are predictive of outcome in patients who undergo external beam radiotherapy or brachytherapy for localized prostate cancer.

2 MATERIALS AND METHODS

2.1 Design and population

This retrospective study was conducted at the Georges François Leclerc Center (CGFL) and the François Mitterrand University Hospital of Dijon (France), realized as a continuation of a preliminary work [27].

Between January 2006 and December 2015, 1300 prostate cancer patients underwent a mpMRI at 3 Tesla using the same protocol at the University Hospital.

Patients were selected for this study using the following inclusion criteria:

- Prostate cancer confirmed by sextant biopsies and diagnosed between January 2008 and December 2015
- Radiotherapy or brachytherapy treatment delivered at the Georges François Leclerc Center, with respect to d'Amico classification and international recommendations [3–28]
- At least 5 years of PSA follow up after completion of radiation

Patients were excluded if they had radical prostatectomy, hormones or any other form of local therapy before their prostate radiotherapy or brachytherapy, node or bone metastases, absence of pre-therapeutic mpMRI, absence of follow-up at the CGFL and poor quality mpMRI (metal artifact mainly related to total hip prothesis, patient movement or digestive gas, incomplete MRI) with impossible interpretation.

A clinical examination was performed before the mpMRI in all patients, allowing a T-tumor classification according to the UICC [29] as well as an ultrasound-guided transrectal prostate biopsy and at least one blood PSA level test, in accordance with international recommendations [4]. Patients were then classified according to the d'Amico classification system to adapt work-up and treatment.

Indeed, after discussion on a multidisciplinary tumor board and with respect to d'Amico classification according to the international recommendations [30], each patient was treated either by external beam radiotherapy (EBRT), prostate brachytherapy (BT) or both, with dose escalated intensity-modulated radiotherapy. Men treated with interstitial brachytherapy received a permanent implantation or radioactive iodine seeds in the prostate.

Patients were followed at the CGFL by their radiation oncologist, within 3 months after the completion of radiation, and every 6 months thereafter for 5 years as well as annual consultations over 5 years.

A PSA blood sample was taken every 6 months during a follow-up period of up to 10 years at least.

According to the Phoenix definition, biochemical recurrence was defined as an increased PSA level with nadir + 2ng/ml [31].

2.2 MRI technique and MRS

All patients had a baseline mpMRI performed at 3 Tesla, with an only pelvic coil, as described previously [32].

Each mpMRI included at least one 3D T2 TSE volumetric sequence and two functional sequences including diffusion-weighted images (DWI) using two values of b (b200-b800) and dynamic contrast enhanced (DCE) T1-weighted images allowing the realization of perfusion curves and the study of the wash-in dynamics (Protocol meeting international recommendations) [16–17].

A 3 Tesla whole body magnet (Siemens Magnetom Trio TIM, Erlangen, Germany) was used with a pelvic multichannel phased-array coil (eight channels). A 3-mm -slice T2-weighted fast spin-echo sequence with a nominal pixel size of 0.9 mm (repetition time, 3400 ms; TE, 85 ms; and echo train length, 13) was used to acquire images in oblique, sagittal, and coronal planes oriented parallel to the prostate peripheral zone-rectal wall axis. Three-dimensional (3D) T2-weighted fast spin-echo (repetition time 3000 ms; echo time 143 ms; echo train length, 109; and slice thickness, 1.5 mm) axial images were then acquired in an oblique axial plane oriented perpendicular to the prostate peripheral zone-rectal wall axis. The nominal matrix and field of-view of the 3D T2-weighted images were respectively 384x308 and 280x240 mm^2, thereby affording submillimetric pixel resolution within the imaging plane. This same image acquisition protocol was used for all patients of the cohort.

Three-dimensional proton MRSI was performed by using a water- and lipid-suppressed double spin-echo point-resolved spectroscopic sequence (PRESS). The volume for MRSI was

selected to maximize coverage of the prostate while minimizing inclusion of rectal air and periprostatic fat.

A representative slice (or series of slices) was chosen for each tumor on the T2 sequence and the concentrations (in mmol-L^{-1}) of Choline (Cho) and Citrate (Cit) were reported in a number of voxels located in tumor and healthy tissue. The actual number of voxels studied depended on the tumor volume. Choline and Citrate are two important metabolites in prostate function but also in tumor [33]. The data collection was carried out in both central zone (CZ) and peripheral zone (PZ) for each patient.

Ratios for Choline to Citrate (Cho/Cit) were automatically calculated for every voxel.

The MRI parameters studied were: the size and volume of the prostate and the number of tumors. In healthy tissue, the apparent diffusion coefficient (ADC) and the wash-in were measured in healthy prostate peripheral zone (PZ) and in healthy central zone (CZ) tissues.

For each tumor lesion visualized, several parameters were studied: the largest tumor size in T2 TSE, the location (apex, middle, base on PZ, CZ or SFMA), the presence of extra capsular effraction (ECE) and its length, tumor ADC and size at b800 on DWI, the average of the lowest 10% of ADCs within the lesion, tumor wash-in, tumor perfusional curve classified from 1 to 3.

Extracapsular invasion has already been defined in other preliminary studies [13].

Finally, each lesion was classified according to its MRI tumor stage and the PIRADS v2 score.

An experienced radiologist (with more than 13 years of experience) who was trained in an expert center (that performs a minimum of 400 prostate mpMRI per year) evaluated all MRI. Two other radiologists in mpMRI prostate training have independently, blinded from the first report and from the patient's treatment and follow-up, assessed all MRI.

The image analysis was performed with Syngo.via software and Image.J software.

2.3 Statistical analysis

Qualitative variables were described using percentages and quantitative variables using means with standard deviations and medians with range. Survival curves were obtained using the Kaplan Meier method and compared with a log rank test. Independent correlates

of biochemical free survival were determined in multivariate Cox regression models. Indeed three models have been used with the following independent variables: NCCN-MRI, PI-RADS v2 and extra-capsular effraction. Variables eligible for multivariate analyses were selected from univariate analyses (threshold to enter multivariate model = 0.20) and had a p-value of less than 0.05. All tests were two-sided and significance threshold was fixed at 5%. Analyses were performed using SAS 9.4.

3 RESULTS

3.1 Description of the population

Two hundred and firty (230) patients were included retrospectively in this study. The mean age of patients at diagnosis was 67.5 (6.7) years.
According to d'Amico classification, 99 (43%) patients were classified as low risk, 82 (35.7%) as intermediate risk and 49 (21.3%) as high risk.
Similarly, for the NCCN classification, 99 (43%) patients were classified as low risk, 97 (42.2%) as intermediate risk, 29 (12.6%) as high risk and 5 (2.2%) as very high risk.

One hundred and fifty six (156) patients were treated by EBRT while 73 patients underwent a permanent implant with iodine seeds as monotherapy and 8 as a brachytherapy boost. Patients treated with EBRT only received a median total dose of 78 Grays (Gy) [46-132 Gy] and those with BT a median total dose of 160 Gy [60-196 Gy]. Forty four (44) patients (19%) had a complementary androgen deprivation therapy in combination treatment.

In this study, the 36 (16%) observed recurrences were composed of 45.9% Gleason 6 and with significantly more-higher Gleason, for example 40.5% of Gleason 7 (29.7% of 3+4), 5.5% of Gleason 8, 2.7% of Gleason 9 or 10 (p=0.066).
Patients who relapsed also had a significantly higher initial clinical T stage (18.9% T3a, 10.8% T2c, 2.7% T3b; p=0.0389).
The initial characteristics of patients are described in Table 1.

Age at diagnostic (years) :	
N=230 Mean : 67.5 (6.7)	Median : 68.0 [52.0 - 83.0]
Clinical T-stage :	
T1c : 119 (51.7%) T2a : 34 (14.8%) T2b : 35 (15.2%)	T2c : 22 (9.6%) T3a : 19 (8.3%) T3b : 1 (0.4%)
Gleason total :	
4 : 1 (0.4%) 5 : 2 (0.9%) 6 : 150 (65.2%) 7 : 70 (30.4%) 3+4 : 49 (21.3%)	8 : 3 (1.3%) 9 : 3 (1.3%) 10 : 1 (0.4%) 4+3 : 20 (8.7%)
Pre-treatment PSA (ng/ml):	
Mean : 11.4 (17.2)	Median : 7.5 [1.4 - 225.0]
D'Amico risk group :	
Low risk : 99 (43.0%) Intermediate risk : 82 (35.7%) High risk : 49 (21.3%)	
NCCN risk group :	
Low risk : 99 (43.0%) Intermediate risk : 97 (42.2%)	High risk : 29 (12.6%) Very high risk : 5 (2.2%)
Treatment :	
EBRT : 105 (45.9%) **BT :** 72 (31.4%) **BT+ HT :** 1 (0.4%)	**EBRT + HT :** 43 (18.8%) **EBRT + BT :** 7 (3.1%) **EBRT + BT + HT :** 1 (0.4%)
Post treatment PSA nadir (ng/ml) :	
Mean : 0.4 (1.4)	Median : 0.2 [0.0 - 18.0]
Latest news status :	
Alive : 201 (87.4%)	Dead : 29 (12.6%)
Disease-related death :	
Yes : 1 (3.7%)	
Biochemical recurrence :	
Yes : 37 (16.1%)	
Localisation of recurrence :	
Local : 22 (59.5%) Régional : 4 (10.8%)	Metastatic : 10 (27.0%) Unknown : 1 (2.7%)
Delay between diagnostic and recurrence (years) :	
Mean : 6.1 (2.6)	Median : 6.0 [2.1 - 11.6]

Prostatic Specific Antigen (PSA), external beam radiotherapy (EBRT), brachytherapy (BT), hormonotherapy (HT)

Table 1: Clinical and demographics characteristics

3.2 MRI and spectroscopic analyses

All MRI were realized after the histological diagnostic of cancer.

The mean prostatic volume on mpMRI was 51.7 (6.0) ml. One hundred and eighty seven (187) patients had a single lesion identifiable by mpMRI, fifteen (15) had two visible lesions and 28 had no visible lesion. A total of two hundred and seventeen (217) lesions were therefore detected on mpMRI.

One hundred and thirteen (113) tumors were classified PI-RADS 5/5, 72 PI-RADS 4/5 and 31 PI-RADS 3/5. Those lesions that were not detectable were classified as PI-RADS 1/5 or 2/5 (existence of benign lesions).

We observed some significant differences between the mpMRI data of patients who relapsed and the others. Indeed, the size of the tumor was larger ($p=0.0019$) and there was more often two tumor lesions detected ($p=0.0286$). Moreover, we noticed that 61.1% of recurrence had an extra capsular effraction ($p<0.0001$) and the mean invasion thickness was measured at 4.9 mm ($p=0.0019$).

There was no significant difference with the extension to seminal vesicles ($p=0.2024$), nor with the spectroscopic data, notably with the increase in the Cho/Cit ratio for tumors in the PZ ($p=0.6122$).

The details of the mpMRI parameters are available in Table 2, the comparison data between patients with and without recurrence is presented in the Table 3 and the initial spectroscopic analyses in Table 4.

	No recurrence	Recurrence	p-value
N	193	37	
Number of lesions:			
1	156 (80.8%)	31 (83.8%)	**0.0286**
2	10 (5.2%)	5 (13.5%)	
Tumor size (mm) :			**0.0019**
Mean	16.9 (8.6)	21.3 (8.8)	
Median	15 [5.0 - 46.0]	20 [7.0 - 41.0]	
Seminal vesicles extension:	6 (3.6%)	3 (8.3%)	**0.2024**
Capsular contact :	137 (82.5%)	31 (86.1%)	0.6027
Contact capsular length (mm):			**0.0006**
Mean	13.3 (9.0)	19.7 (10.8)	
Median	10.0 [2.0 - 42.0]	19.0 [5.0 - 42.0]	
Extra capsular effraction :	33 (19.9%)	22 (61.1%)	**< 0.0001**
Effraction thickness (mm) :			**0.0019**
Mean	3.3 (1.1)	4.9 (1.9)	
Median	3.0 [1.0 - 5.0]	4.2 [2.0 - 9.0]	
Tumor ADC (s/mm²) :			**0.0427**
Mean	885.3 (266.6)	784.6 (277.7)	
Median	852.0 [197.0 - 1646.0]	717.0 [242.0 - 1604.0]	
Tumor DWI size (mm) :			**0.0045**
Mean	15.1 (8.1)	18.5 (7.7)	
Median	13.0 [0.0 - 49.0]	18.0 [8.0 - 37.0]	
Wash-in :			**0.0411**
Mean	223.0 (76.0)	248.5 (62.3)	
Median	223.0 [27.0 - 608.0]	237.5 [125.0 - 393.0]	
MRI T-stage :			**< 0.0001**
T1c	28 (14.5%)	1 (2.4%)	
T2a	91 (47.2%)	9 (22.0%)	
T2b	33 (17.1%)	5 (13.5%)	
T2c	10 (5.2%)	2 (5.4%)	
T3a	25 (13.0%)	19 (51.4%)	
T3b	6 (3.1%)	3 (8.1%)	
NCCN risk group :			**< 0.0001**
Low	81 (42.0%)	4 (10.8%)	
Intermediate	72 (37.3%)	10 (27.0%)	
High	32 (16.6%)	18 (48.6%)	
Very high	8 (4.1%)	5 (13.5%)	

Apparent diffusion coefficient (ADC), diffusion weighted images (DWI)

Table 3: Comparison mpMRI parameters between recurrence population and others

	Citrate (mmol/l)	**Choline** (mmol/l)	**Cho/Cit** (mmol/l)
Healthy tissue CZ	N= 221 Mean: 15.4 (7.3) Median: 15.0 [0.3 - 37.7]	N= 221 Mean: 2.5 (0.8) Median: 2.5 [0.4 - 4.9]	N= 221 Mean: 0.3 (1.0) Median: 0.2 [0.0 - 13.7]
Tumor CZ	N= 15 Mean: 9.7 (5.2) Median: 10.3 [3.0 - 20.4]	N= 15 Mean: 3.1 (0.8) Median: 3.1 [1.8 - 4.6]	N=15 Mean: 0.5 (0.4) Median: 0.3 [0.1 - 1.5]
Healthy tissue PZ	N= 222 Mean: 19.6 (8.5) Median: 19.7 [1.4 - 47.5]	N= 222 Mean: 2.3 (0.7) Median: 2.4 [0.7 - 4.5]	N= 222 Mean: 0.2 (0.2) Median: 0.1 [0.0 - 1.7]
Tumor PZ	N= 182 Mean: 11.1 (5.9) Median: 11.2 [0.1 - 27.8]	N= 182 Mean: 2.8 (1.4) Median: 2.7 [0.3 - 8.8]	N= 182 Mean: 0.7 (2.7) Median: 0.2 [0.0 - 35.0]

Central zone (CZ), peripheral zone (PZ)

Table 4: Initial spectroscopic analyses

3.3 Evolution of prognostic groups after mpMRI

We compared the initial clinical T-stage and the MRI T-stage obtained to redefine the NCCN MRI risks groups.

Firstly, the analysis of the comparison between clinical T-stage and MRI T-stage showed that after mpMRI 128 (55%) patients moved to a higher MRI T-stage than their initial clinical T-stage. Seventy eight (78 (34%)) patients did not change their stage and 24 (10.4%) moved to a lower MRI T-stage than their clinical T-stage.

The same was true for the comparison between the NCCN and the NCCN-MRI classification: 50 (21.7%) patients were upgraded to a higher risk group after MRI, 169 (73.4%) remained in the same NCCN-MRI risk group as their clinical NCCN risk group and 11 (4.7%) were downgraded to a lower risk group.

Thus, 85 (36.9%) patients were classified as low risk according to NCCN-MRI, 82 (35.6%) patients in the intermediate group, 50 (21.7%) in high risk and 13 (5.6%) in the very high risk group, summarized in the Figure 1.

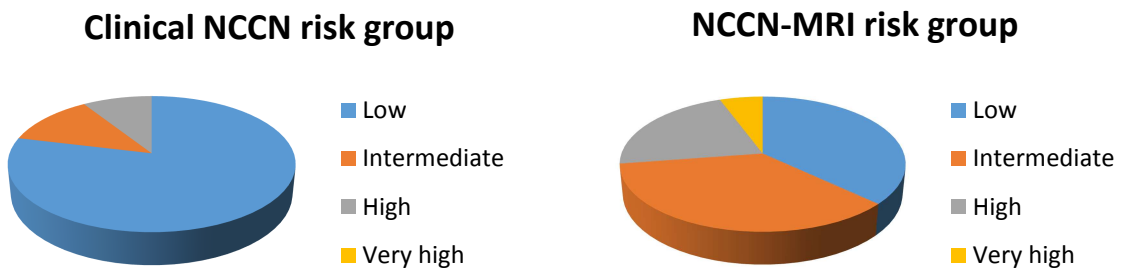

Figure 1 Proportion of patients before and after MRI analyses

3.4 Univariate and multivariate analysis of biochemical relapse-free survival

The median follow-up time since the date of diagnostic was 8.7 years [1.6 – 13.2] and the overall survival rate was 88.4% [95%CI: 83.4% - 92.0%] at 5 years and 62.9% [95%CI: 53.7% - 70.8%] at 10 years (Figure 2).

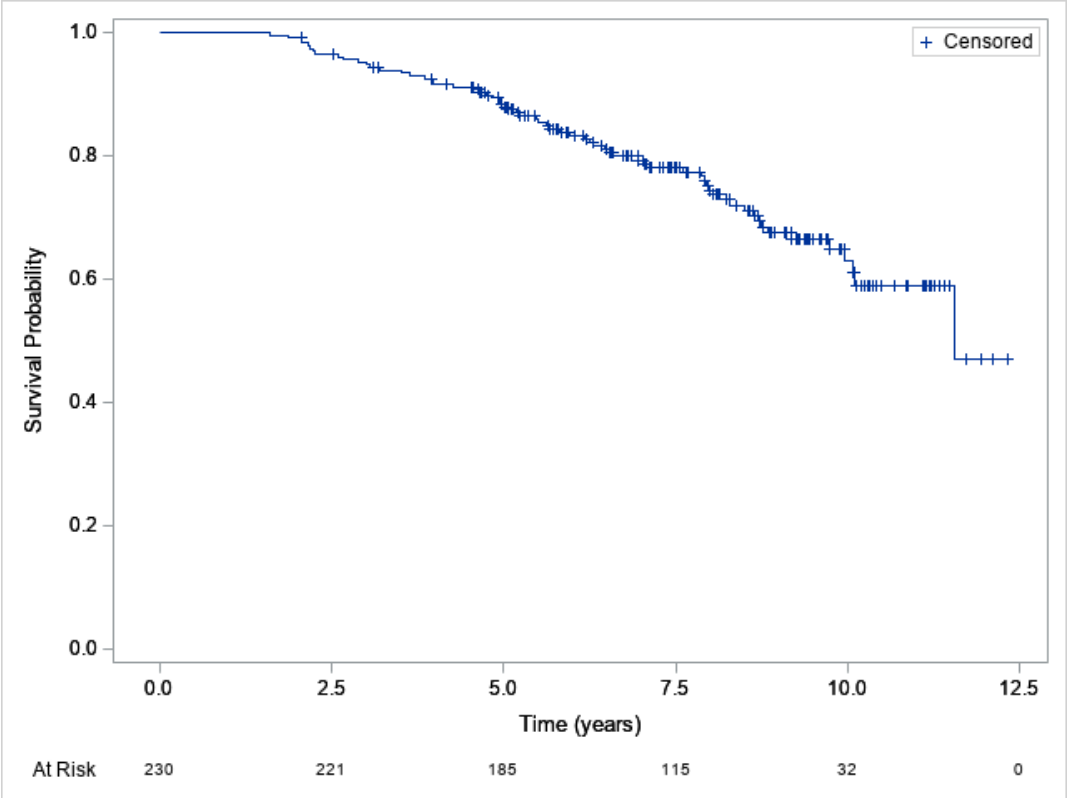

Figure 2 Biochemical relapse-free survival

A summary of the univariate analysis is available in Table 5 and the different models used in the multivariate analysis are summarized in Table 6.

Variable	HR	CI 95%	p-value
Clinical T-stage: N=230			
T2 vs T1c	1.811	[1.055 -3.110]	**0.0323**
T3 vs T1c	2.359	[1.120 – 4.965]	
PSA max pre-treatment (ng/ml): N=230			**0.0031**
>7.5 vs ≤ 7.5	2.205	[1.306 – 3.725]	
Gleason: N=230			
≥ 4+3 vs ≤ 3+4	2.014	[1.094 – 3.706]	**0.0245**
7-10 vs 4-6	2.256	[1.38 – 3.689]	**0.0012**
Clinical d'Amico risk group: N=230			
High vs low	3.01	[1.586 – 5.711]	**0.0030**
Intermediate vs low	2.171	[1.159- 4.069]	
Clinical NCCN risk group: N=230			
High & very high vs low	2.634	[1.282 – 5.410]	**0.0063**
Intermediate vs low	2.454	[1.354 – 4.448]	
D'Amico-MRI risk group: N=230			
High vs low	5.583	[2.692 – 11.576]	**<.0001**
Intermediate vs low	2.465	[1.107 – 5.490]	
NCCN-MRI risk group: N=230			
High vs low	5.803	[2.735 - 12.312]	**<.0001**
Intermediate vs low	2.477	[1.127 - 5.442]	
Very high vs low	6.797	[2.526 - 18.288]	
Wash in ZC: N=230			
> 170 vs ≤ 170	0.462	[0.271-0.787]	**0.0045**
Tumor size (mm): N=230			
>15mm vs ≤ 15	2.460	[1.415 - 4.279]	**0.0014**
Extra capsular effraction: N=230			
Yes vs no	3.672	[2.206 - 6.110]	**<.0001**
Tumor ADC (s/mm²): N=230			
>-640 vs ≤640	0.538	[0.313 - 0.922]	**0.0241**
Tumor DWI size (mm): N=230			
≥14 vs < 14	2.562	[1.502 - 4.370]	**0.0006**
MRI T-stage: N=230			
T2 vs T1c	1.509	[0.529 - 4.305]	**<0.0001**
T3 vs T1c	5.161	[1.823 - 14.609]	
PI-RADS v2 : N=230			
4-5 vs 1-3	3.372	[1.454 - 7.820]	**0.0046**
Choline in tumor PZ voxel most affected: N=273			
>3 vs ≤ 3	2.274	[1.275 - 4.056]	0.0054
Choline/Citrate tumor PZ: N=171			
>0.15 vs ≤ 0.15	2.061	[0.879 - 4.832]	0.0961
Choline/Citrate healthy tissue PZ: N=208			
>0.25 vs ≤ 0.25	2.092	[1.082 - 4.043]	**0.0282**

Choline/Citrate healthy tissue			
CZ: N=207			
>0.1 vs ≤ 0.1	2.972	[1.186 - 7.450]	**0.0201**

Prostate specific antigen (PSA), National Comprehensive Cancer Network (NCCN), magnetic resonance imaging (MRI), apparent diffusion coefficient (ADC), diffusion weighted images (DWI), Prostate Imaging Reporting and Data System version 2 (PI-RADS v2), central zone (CZ), peripheral zone (PZ)

Table 5: Univariate analysis of biochemical relapse-free survival

Variable	HR	CI95%	p-value	Harrell C
Model 1 using NCCN-MRI				
N=181				
Choline/Citrate healthy tissue CZ			**0.0378**	
> 0.1 vs ≤ 0.1	2.969	[1.064 - 8.286]		
				0.72
NCCN-MRI			**<.0001**	
Intermediate risk vs low risk	3.067	[1.133 - 8.306]		
High & very high risk vs low risk	7.003	[2.711 - 18.091]		
Wash in ZC			**0.0351**	
> 170 vs ≤ 170	0.513	[0.276 - 0.955]		
Model 2 using extra capsular effraction				
N= 182				
Choline/Citrate healthy tissue CZ			**0,0449**	
> 0.1 vs ≤ 0.1	2.857	[1.024 - 7.970]		0.7
Extra capsular effraction			**<.0001**	
Yes vs No	3.332	[1.936 - 5.736]		
Wash in ZC			**0.0386**	
> 170 vs ≤ 170	0.517	[0.277 - 0.966]		
Model 3 using PI-RADS v2				
N=181				
Choline/Citrate healthy tissue CZ			**0.0333**	
> 0.1 vs ≤ 0.1	3.029	[1.092 - 8.404]		
PIRADS v2			0.0521	
4-5 vs 1-3	7.123	[0.982 - 51.642]		0.67
Wash in CZ			**0.0106**	
> 170 vs ≤ 170	0.447	[0.241 - 0.828]		
Average of the lowest 10% of ADC (mm2/s)			**0.0171**	
> 270 vs ≤ 270	0.481	[0.264 - 0.878]		

National Comprehensive Cancer Networ (NCCN), magnetic resonance imaging (MRI), apparent diffusion coefficient (ADC), Prostate Imaging Reporting and Data System version 2 (PI-RADS v2), Harrell coefficient (HC), central zone (CZ), peripheral zone (PZ)

Table 6: Multivariate analysis of biochemical relapse-free survival

4 DISCUSSION

4.1 Population

The initial demographical characteristics of our patients were conform to data in the literature; In fact, the average age at diagnosis was 67.5 years compared to the average age of 70 years in French cancer registries in 2011 [34].

Our study population represented the heterogeneity of localized prostate cancers, with 51.7% of T1c clinical T-stage, 14.8% of T2a and 9.6% of T2c for example, with histopathological diagnosis of 65.2% of Gleason 6, 30.4% of Gleason 7 and 3% of Gleason 8 and more.

Thus, we had a large proportion of low (43.0%) and intermediate risk (42.2%) patients according to NCCN classification.

The median duration of our follow-up was long (8.7 years [1.6 – 13.2]) compared with many studies where it varies regularly between 36 months and 6 years [35–36–37–38], thus reinforcing the credibility of our concluding observations regarding long term survival in our study.

Survival data at 5 years (88.4%) and 10 years (62.9%) are less favorable than those reported by the French INCA (Institut National du CAncer) in 2021, i.e. 93% at 5 years and 80% at 10 years [39]. This difference can be explained by the improvement of tumor detection techniques, staging and management over the last 10 years.

The relapse rate of prostate cancer after external beam radiotherapy or brachytherapy in our population (16%) was similar to the results of the study conducted by Lazarev et al. in 2018, estimated at 13.9% [40].

Thus, our study population was wholly representative of French prostate localized cancers, particularly those of low and intermediate risk according to the NCCN classification.

4.2 Assessment of prognostic group with MRI

It has been known for a decade that the performance of prostate cancer detection in mpMRI is dependent on tumor volume and the Gleason histological score. Our MRI tumor detection rate was 88.5%, in accordance with the data in the literature after Styles et al. [41] that demonstrated a sensitivity of 85% for the detection of lesions greater than 0.5 cc at 3T MRI. Moreover, a systematic review of 66 studies in 2017 [42] reported detection of index lesions in 90% of cases. This is clearly supported by our results because MRI could detect a significant

lesion in 78% of patients considered as clinical T1c, i.e. in whom the DRE was not pathological, and thus reclassified them in a higher risk group.

More generally, we noted that 152 patients did not have the same concordance between their initial clinical T-stage and their MRI stage, and in particularly 128 patients with a higher MRI T-stage, i.e. a final reclassification of 21.7% of patients into a higher-risk group according to the NCCN classification. These results are consistent with those of Gomez-Iturriage et al. [43] who demonstrated that 38% of patients initially considered T1 or T2 were reclassified T3 MRI and therefore 35% reclassified as high risk after MRI analysis. These results are also suggested in the retrospective study by Counago et al. [44] published in 2015 where 16.7% of the 269 patients initially classified as clinical T1 or T2 were reclassified after MRI analysis as T3 or T4.

It is therefore recognized that MRI has a decisive role in the re-evaluation of the tumor T-stage, and also modifies the prognostic classification of patients by improving the detection of lesions and their characterization.

4.3 Place of mpMRI and spectroscopic analysis in the study of prognostic factors

According to the multivariate analysis, we have identified 3 prognostic elements of biochemical relapse free survival (bRFS) in patients with localized prostate cancer treated by external radiotherapy or brachytherapy: the NCCN-MRI classification, the extra capsular effraction (EEC) and the choline/citrate ratio in healthy CZ tissue.

These results suggest the hypothesis that the T-MRI classification is at least as effective as the T-clinical classification to predict patient outcomes, the traditional NCCN classification not appearing as an independent factor of recurrence in our analysis.

Most studies to date have focused on the prognostic value of MRI at diagnosis in studies where the T-stage and Gleason score are established on prostatectomy specimens [45–46].

This gold standard of tumor T stage cannot be used in studies focused on non-surgical therapies such as radiotherapy where the T stage is still established on the Gleason grade of biopsies and the digital rectal examination.

Our results lead us to consider MRI T stage, and therefore the NCCN MRI classification, as an essential prognostic factor in these situations.

Extra capsular effraction is a recognised prognostic factor [47] reflecting a more aggressive disease, classifying it at least as a T3 stage, with an increased risk of metastatic spread as demonstrated in the study of McKenna et al. [48] where EEC was, with a threshold of 5mm, the only independent factor found for the occurrence of metastasis.

On the other hand, Yu et al. [22] have demonstrated in a retrospective study that the combination of mpMRI and spectroscopic analyses reduced inter-observer variability in the diagnosis of EEC on pre-therapeutic MRI, using the ratio choline/citrate > 2SD to detect tumor boundaries.

In the multivariate analysis, only the choline/citrate ratio in healthy tissue in CZ returned as an independent factor of recurrence, with quite similar risk in all three models. Citrate is an important element in prostate energy metabolism, whose levels vary more significantly than those of choline, which reflects the degree of tumor membrane cell activity [49]. The early decrease in citrate is therefore due to both changes in cellular function and in the organization of the tissue, but may also decrease in prostatitis [50], when the choline level increases proportionally to tumor cell proliferation or in the case of necrosis, a phenomenon which is mainly visible in undifferentiated tumors, particularly with a high Gleason grade [51]. However, in our study, 43% of patients who had relapsed were classified as T1c, lesions that were not visible or too small to be detected by MRI, probably diffusely infiltrating the parenchyma, causing the choline/citrate ratio variation within the whole CZ, without significantly modifying this same ratio within the PZ. In fact, as the PZ is basically richer in citrate due to its glandular nature, Casciani et al. [52] showed that normal concentrations of citrate in this zone were only found in cases of well-differentiated tumors, with a low Gleason grade, a significant drop in citrate being a marker of tumor dedifferentiation. This is in accordance with our population who relapsed, composed mainly of low Gleason grade: 45.9% of Gleason 6 and 40.5% of Gleason 7 (29.7% of 3+4).

Thus, spectroscopic analysis can be a useful tool to assess tumor differentiation and biological aggressiveness.

Not surprisingly, a high PI-RADS v2 score (4 or 5) is significantly ($p=0.02$) associated with lower ADC values, reflection of increased tumor cellularity, as demonstrated in Nagarajan et al. study [53] with a strong positive correlation between ADC and tumor volume ($p= 0.018$).

The tumor size in T2 sequence, the signal and tumor size in DWI are often used in routine to evaluate tumor characteristics failing to assess the patient's prognosis.

The univariate analysis showed a significant difference for tumor size with a cut off at 15 mm (p= 0.0014) and for the tumor DWI size with a smaller cut off at 14 mm (p= 0.0006), unconfirmed in multivariate analysis and thus nonintegrated into the mpMRI prognostic factors. This result could be confirmed by a larger cohort to define a tumor size as a risk of recurrence, both in T2 sequence and DWI imaging.

Thus, all these results confirm the usefulness of realizing an initial mpMRI in our population, by improving the detection and characterisation of tumors, particularly their aggressiveness. A prognostic classification including both initial clinical data and MRI analysis seems to be more appropriate to define better treatment.

However, our study has some limitations. We noted that the wash-in variable in the CZ emerged significantly with almost the same risk in the 3 models (HR=0.5) as a prognostic factor for recurrence, without being able to explain this result in the literature, probably corresponding to a statistical error in our study. It seems difficult to interpret the value of this isolated parameter without a parallel wash-out study. Besides, it is a monocentric retrospective study which remains limited, needing our results to be confirmed by a global study integrating more centers. Moreover, it will be interesting to include more patients classified as high risk according to the NCCN classification, with an increased risk of metastasis and worse prognostic.

The major strengths of our study rely on the homogeneity of MR acquisition and interpretation of images by an experienced team and protocolised treatments delivered in an academic center specialized in cancers.

5 CONCLUSION

The combination of mpMRI and spectroscopy has shown in our retrospective study including 230 patients from January 2008 to December 2015 the key role played in the initial management of localized prostate tumors treated by radiotherapy or brachytherapy, particularly in tumor staging, and thus, largely in the choice of therapy. Moreover, we were able to define 3 prognostic elements of survival without biochemical recurrence more accurate than clinical variables, which are the NCCN-MRI classification, the choline/citrate ratio in healthy tissue in CZ and extra-capsular effraction

It would then be interesting to propose a multicenter study with a larger population to reinforce the link between these different elements.

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THESE SOUTENUE PAR M.....elle Audrey ASUNCION

CONCLUSIONS

L'association IRM multiparamétrique et analyse spectroscopique a montré dans notre étude rétrospective incluant 230 patients de janvier 2008 à décembre 2015 qu'elle tenait une place décisive dans la prise en charge initiale des tumeurs localisées de prostate traitées par radiothérapie externe ou curiethérapie, particulièrement dans l'extension tumorale, et donc en grande partie dans le choix thérapeutique. De plus, nous avons pu définir 3 éléments pronostics de survie sans rechute biochimique plus précis que des variables cliniques, qui sont la classification NCCN-IRM, le rapport choline/citrate dans le tissu sain en zone transitionnelle et l'envahissement extra-capsulaire.

Il serait alors intéressant de proposer une étude multicentrique avec une plus grande population pour conforter le lien entre ces différents éléments.

Le Président du Jury,

Pr. LOFFROY

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

Pr. M. MAYNADIE

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ANNEXES

Prostatic volume (ml) :	
Mean : 51.7 (20.7)	Median : 46.7 [13.8 - 135.7]
Tumor size (mm) :	
Mean : 17.5 (8.6)	Median : 15.0 [5.0 - 46.0]
Tumor location :	
PZ : 191 (88.4%) CZ : 24 (11.1%)	SFMA : 1 (0.5%)
Extension to seminal vesicles :	
No : 221 (96%)	Yes : 9 (4%)
Capsular contact :	
No : 34 (16.8%)	Yes : 168 (83.2%)
Contact length (mm) :	
Mean : 14.5 (9.6)	Median : 11.0 [2.0 - 42.0]
Extra-capsular effraction (ECE) :	
No : 147 (72.8%)	Yes : 55 (27.2%)
Thickness of ECE (mm) :	
Mean : 3.9 (1.6)	Median : 4.0 [1.0 - 9.0]
Tumor ADC (mm^2/s) :	
Mean : 867.4 (270.7)	Median : 842 [197.0 - 1646.0]
Average of the lowest 10% of ADC (mm^2/s) :	
Mean : 526 (255.3)	Median : 501.0 [0.0 - 1288.0]
Tumor signal DWI (b800) :	
Hypersignal : 130 (60.2%)	Isosignal : 86 (39.8%)
Tumor size DWI (mm) :	
Mean : 15.5 (8.0)	Median : 14.0 [0.0 - 49.0]
Wash-in :	
Mean : 226.7 (73.9)	Median : 224.0 [27.0 - 608.0]
MRI T-stage :	
T1c : 29 (12.6%) T2a : 98 (42.6%) T2b : 38 (16.5%)	T2c : 12 (5.2%) T3a : 44 (19.1%) T3b : 9 (3.9%)
Risk group according to D'Amico-MRI :	
Low : 85 (37%) Intermediate : 72 (31.3%)	High : 68 (34.2%)
Risk group according to NCCN-MRI:	
Low : 85 (37%) Intermediate : 82 (35.7%)	High : 50 (21.7%) Very high : 13 (5.7%)
PI-RADS v2 :	
1-2 : 28 (12.1%) 3 : 26 (11.3%)	4 : 70 (30.4%) 5 : 106 (46.1%)

Extra capsular effraction (ECE), apparent diffusion coefficient (ADC), diffusion weighted images (DWI), Prostate Imaging Reporting and Data System version 2 (PI-RADS v2)

Table 2: mpMRI parameters

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TITRE DE LA THESE :

Prédiction de la récidive dans le cancer de prostate après radiothérapie à l'aide de l'IRM multiparamétrique et de l'imagerie spectroscopique : évaluation de facteurs pronostiques sur l'imagerie pré-thérapeutique

PREDICTION OF PROSTATE CANCER RECURRENCE AFTER RADIATION THERAPY USING MULTIPARAMETRIC MRI AND MR SPECTROSCOPIC IMAGING: ASSESSMENT OF PROGNOSTIC FACTORS ON PRETREATMENT IMAGING

AUTEUR : AUDREY ASUNCION

RESUME :

Objectif : Evaluer si certains résultats de l'IRM initiale pré-thérapeutique combinée à l'étude spectroscopique sont des facteurs prédictifs de récidive biochimique chez les patients atteints de cancers localisés de prostate traités par radiothérapie externe ou curiethérapie.

Matériel et méthode : Nous avons inclus dans notre étude rétrospective monocentrique de janvier 2008 à décembre 2015 230 patients traités par radiothérapie externe ou curiethérapie, ayant eu une IRM initiale multiparamétrique avec étude spectroscopique au Centre Georges François Leclerc ou au CHU de DIJON pour néoplasie prostatique localisée, prouvée histologiquement. Deux radiologues entrainés ont enregistré la présence de tumeur, le stade T IRM ainsi que les anomalies métaboliques pour chaque IRM avec étude spectroscopique. Des analyses de Cox univariées et multivariées ont explorés la relation entre des variables cliniques et d'imagerie pour mettre en évidence des facteurs pronostiques de récidive, en utilisant comme critère de jugement principal la rechute biochimique.

Résultats : L'analyse IRM a permis de reclasser 21,7% des patients dans un groupe NCCN IRM plus élevé que leur T clinique initial mais aussi de détecter une lésion chez 78% des patients considérés comme T1c clinique. Après une durée moyenne de suivi de 8,7 ans [1,6 -13,2] après le diagnostic de cancer, 36 (16%) patients ont développé une rechute biochimique. L'analyse de Cox multivariée a démontré l'existence de 3 facteurs indépendants de récidive biochimique qui sont l'envahissement extra capsulaire (HR=3,33; 95%IC 1,93-5,73; p<,0001), le rapport choline/citrate dans le tissu sain en zone transitionnelle (HR=2,96; 95%IC 1,06-8,28; p=0,04) et la classification NCCN IRM (intermédiaire vs faible risque HR=3,06; 95%IC 1,13-8,30; p< ,0001).

Conclusion : L'association IRM multiparamétrique et analyse spectroscopique a montré qu'elle tenait une place décisive dans la prise en charge initiale des tumeurs localisées de prostate traitées par radiothérapie ou curiethérapie, notamment dans l'extension tumorale. Nous avons également pu définir 3 éléments pronostics de survie sans rechute biochimique qui sont la classification NCCN-IRM, le rapport choline/citrate dans le tissu sain en zone transitionnelle et l'envahissement extra-capsulaire.

MOTS-CLES : PROSTATE, CANCER, IMAGERIE PAR RESONANCE MAGNETIQUE, SPECTROSCOPIE, GLEASON, RADIOTHERAPIE