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Cécilia LEGER

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TITRE

Impact de la TEP-TDM au (68)Ga-PSMA, après une TEP-TDM au (18)F-Choline négative, sur la décision de traitement et le contrôle du PSA, chez les patients présentant une réascension du PSA après un traitement local à but curatif pour un cancer de prostate : une étude cas-témoins comparative monocentrique.

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Impact de la TEP-TDM au (68)Ga-PSMA, après une TEP-TDM au (18)F-Choline négative, sur la décision de traitement et le contrôle du PSA, chez les patients présentant une réascension du PSA après un traitement local à but curatif pour un cancer de prostate : une étude cas-témoins comparative monocentrique.

Résumé

La prise en charge de la réascension du PSA, après un traitement local à but curatif du cancer de prostate, a beaucoup évolué avec l'arrivée des techniques d'imagerie nucléaire permettant une meilleure détection de la localisation des récidives. Cependant, l'impact clinique à long terme des décisions de traitement en résultant reste à déterminer.

L'objectif de cette étude est d'évaluer le bénéfice d'une stratégie de traitement basée sur les résultats de la TEP-TDM (68)Ga-PSMA après une TEP-TDM (18)F-Choline négative.

Nous avons mené une étude rétrospective cas-témoins. Nous avons inclus 28 patients ayant bénéficié d'une TEP-TDM au (68)Ga-PSMA pour une réascension des PSA et, dans le groupe « Contrôle », 36 patients traités avant l'arrivée de la TEP-TDM au (68)Ga-PSMA, qui avaient eu une TEP-TDM au (18)F-Choline négative lors de la réascension du PSA.

Les résultats de la TEP-TDM au (68)Ga-PSMA ont modifié la décision thérapeutique pour 79% des patients. Le changement le plus fréquent était de débuter un traitement actif (radiothérapie pour 2/3 des patients et hormonothérapie pour 1/3 des patients) au lieu de poursuivre la surveillance. Le critère de jugement principal était la survie sans événement, définie comme l'intervalle de temps entre la TEP-TDM et la progression du PSA et/ou le changement de ligne de traitement. Celle-ci n'était pas statistiquement différente entre les deux groupes (p=0,58). La survie sans hormonothérapie était significativement plus courte dans le groupe PSMA (médiane de 10 mois contre 35 mois dans le groupe témoin, p=0,003). Le taux de réponse des PSA était de 60,7% dans le groupe PSMA contre 41,7% dans le groupe contrôle (p=0,31).

La TEP-TDM au (68)Ga-PSMA a induit un changement de traitement pour la majorité des patients, mais notre étude ne met pas en évidence de bénéfice clinique de la stratégie de traitement en résultant. Des études ayant un effectif plus important et un suivi plus long sont nécessaires pour confirmer ces résultats.

Impact of (68)Ga-PSMA PET/CT after a negative (18)F-Choline PET/CT on treatment decision and PSA control for Prostate Cancer patients with rising PSA after local treatment: a monocentric comparative case-control study.

Abstract

Management of rising PSA after a local treatment with curative intent for a prostate cancer has greatly evolved since the arrival of nuclear imaging techniques allowing a more efficient restaging. Yet, long-term clinical impact of the treatment strategy based on PET/CT results remains to be determined. The objective of this study is to assess the benefit of a treatment strategy based on the results of a (68)Ga-PSMA PET/CT after a negative (18)F-Choline PET/CT.

We conducted a monocentric retrospective case-control study. We included 28 patients who underwent a (68)Ga-PSMA PET/CT for rising PSA and, in the Control group, 36 patients treated prior to the arrival of (68)Ga-PSMA PET/CT who had a negative (18)F-Choline PET/CT when they presented with rising PSA.

(68)Ga-PSMA PET/CT results changed the anticipated treatment for 79% of patients. The most frequent change was the start of an active treatment instead of going on with the surveillance (radiotherapy for 2/3 of patients and Androgen Deprivation Therapy (ADT) for 1/3 of patients). The primary endpoint was the Event-Free Survival (EFS), defined as time from PET/CT to PSA progression and/or change of treatment. EFS was not statistically different between the two groups (p=0.58). ADT Free Survival was significantly shorter in the PSMA group (median of 10 months versus 35 months in the control group, p=0.003). PSA response rate was 60.7% in the PSMA group versus 41.7% in the Control group (p=0.31).

(68)Ga-PSMA PET/CT impacted therapeutic management of rising PSA for the majority of the patients but the subsequent treatment strategy did not demonstrate clinical benefit in our study. Studies with a larger population and longer follow up are needed to confirm these results.

Mots clés :

Cancer de Prostate

Récidive biochimique

Ascension du PSA

TEP-TDM au (68)Ga-PSMA

TEP-TDM au (18)F-Choline

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En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre

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Liste des abréviations

ADT	Androgen Deprivation Therapy
ATU	Authorisation Temporaire d'Utilisation
BCR	Biochemical Recurrence
CR	Complete Response
CT	Computed Tomography
dPFS	Distant Progression Free Survival
EFS	Event Free Survival
Gy	Gray
ISUP	International Society of Urological Pathology
MDT	Metastasis Directed Therapy
MPR	Major Partial Response
MRI	Magnetic Resonance Imaging
NA	Non Assessable
OS	Overall Survival
PCWG2	Prostate Cancer Working Group 2
PD	Progressive Disease
PET/CT	Positron Emission Tomography/Computed Tomography
PR	Partial Response
PSA	Prostate-Specific Antigen
PSA DT	PSA doubling time
PSMA	Prostate-Specific Membrane Antigen
RT	Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SD	Stable Disease

Impact of (68)Ga-PSMA PET/CT after a negative (18)F-Choline PET/CT on treatment decision and PSA control for Prostate Cancer patients with rising PSA after local treatment: a monocentric comparative case-control study.

Background

For patients newly diagnosed with localised prostate cancer, the two main treatment options with curative intent are radical prostatectomy or radiotherapy. In the following months or years, 27 to 53% of patients present with rising PSA levels without any target lesion detected using traditional imaging (pelvic MRI, thoraco-abdominopelvic CT, and technetium bone scans)(1). This biochemical recurrence (BCR) indicates an occult re-occurrence of the disease. Although a rising PSA level precedes detectable metastases by an average of 7 to 8 years, there is no clear correlation between BCR alone and prostate cancer specific mortality(2). Therefore, the challenge in treating BCR is to delay or prevent the emergence of metastases while limiting quality of life deterioration due to treatment toxicity and avoiding overtreatment of indolent diseases.

Current European guidelines are equivocal as to the best management of BCR. They recommend surveillance for low risk patients and early salvage radiotherapy for intermediate or high risk patients, or Androgen Deprivation Therapy (ADT) for patients with a PSA doubling time under 12 months(3). Those recommendations are based on publications where restaging at BCR was performed using traditional imaging only, which show poor performances below a PSA value of 10 ng/ml.

However, emerging high-performance nuclear imaging techniques, such as (18)F-Choline PET/CT and (68)Ga-PSMA PET/CT, have recently made it possible to better define this very heterogeneous population and perform a more accurate restaging. Using these new radiotracers, we now know that the BCR terminology actually regroups a wide variety of clinical presentations with different prognosis: pelvic recurrence, extra-pelvic lymph node recurrence, bone or visceral metastatic recurrence, oligo or multimetastatic. Thus, attempts at a unicist therapeutic response to BCR (salvage pelvic radiotherapy or ADT) have had so far only a limited impact on overall survival (OS).

(18)F-Choline PET/CT was the first available nuclear exam in clinical routine and has now replaced traditional imaging exams at BCR because of its superior sensitivity of 86% and specificity of 93%(4). It is usually performed when PSA reaches 2 ng/ml (or above 1ng/ml when PSA doubling time is short). It has helped clinicians to customize the therapeutic proposal according to the lesions detected, but long-term clinical impact of this strategy remains to be determined.

(68)Ga-PSMA PET/CT has shown even superior performances with positive results at PSA levels as low as 0.2 ng/mL and revealing up to 39% additional lesions compared to radiolabeled Choline PET/CT(5,6). In France, Temporary Authorization for Use (ATU) imposes a sequential use of the nuclear exams: (68)Ga-PSMA PET/CT can only be performed after a negative or equivocal (18)F-Choline PET/CT.

Several studies have shown that the results of a (68)Ga-PSMA PET/CT led to changes in clinical practice for 20 to 75% of patients: abandonment of the salvage radiotherapy project or modification of radiation fields, loco-regional treatment of oligometastases, delay in the onset of ADT(7,8). However, in the context of a mostly slowly progressive disease with prolonged survival, the literature demonstrating that these changes improve overall survival is slow to emerge.

The objective of this study is to determine whether the (68)Ga-PSMA PET/CT image-oriented treatment strategy provides a benefit when (18)F-Choline PET/CT is negative.

Methods

1. Study design and population

We conducted a retrospective comparative case-control observational study at the University Hospital of Tours.

Patients were eligible for enrolment if they met the following criteria: histologically confirmed prostate cancer previously treated with curative intent, rising PSA, negative or inconclusive (18)F-Choline PET/CT, age 18 or older.
Rising PSA was defined as two consecutive PSA values above 0.2 ng/mL after prostatectomy, or two consecutive values above nadir + 2 ng/mL after radiotherapy.

We enrolled patients in two groups. The first group called “PSMA group” included patients with a rising PSA who underwent a (68)Ga-PSMA PET/CT after a negative or inconclusive (18)F-Choline PET/CT according to the ATU’s conditions. The second group called “Control group” included patients treated prior to the arrival of (68)Ga-PSMA PET/CT (before 2019), who had a negative or inconclusive (18)F-Choline PET/CT when they presented with rising PSA.

Patients with known multimetastatic disease at the time of PET/CT and for whom PET/CT was performed for initial staging were not included.

We collected the following clinical data at enrolment: population characteristics and initial prognostic parameters, type of curative treatment, time to BCR, results of (68)Ga-PSMA PET/CT if performed and type of treatment carried out after PET/CT. We collected follow up PSA levels after PET/CT for both groups.

For each patient in the PSMA group, the clinical situation was discussed in a multidisciplinary staff meeting without disclosing the (68)Ga-PSMA PET/CT results and the therapeutic proposition was compared to the actual therapeutic attitude recorded in the medical file.

2. Endpoints

The primary endpoint was the Event-Free Survival (EFS), defined as time from PET/CT to PSA progression according to the definition of PCWG2 (PSA increase of at least 25% confirmed by a dosage at least 3 weeks later) and/or change of treatment.

A change of treatment is defined as the introduction of any active treatment if the patient was on surveillance after PET/CT or the start of a new line of treatment, including stereotactic radiotherapy, after the treatment implemented based on PET/CT results.

Secondary endpoint criteria included:

- Change in the therapeutic decision of the multidisciplinary staff meeting after (68)Ga-PSMA PET/CT results
- ADT Free Survival: time from PET/CT to the initiation of intermittent or continuous palliative ADT
- PSA Response Rate: patients exhibiting any kind of PSA response including stability (PSA increase or decrease lower than 25% or unconfirmed by the second dosage)
- Best PSA response amongst: PSA progression (above-mentioned definition), stable PSA (above-mentioned definition), partial response (PSA decrease of at least 25%), major partial response (PSA decrease of more than 50%), complete response (undetectable PSA). Each PSA evolution had to be confirmed by a second dosage.
- Overall survival (OS)

3. Statistical methods

Statistical analyses were made using IBM® software SPSS® Statistics 27.0.1.
Categorial data were analysed using chi-square tests. Continuous numeric data were tested for normality using Shapiro Wilk test and compared using t-test if distribution was normal or Mann Whitney U test or Kruskal Wallis test if not. Survival data were described with the Kaplan and Meier method and compared with the log-rank test.
Association between data with non normal distribution were tested with Kendall' Tau-b correlation coefficient and Spearman's rank correlation coefficient.

Differences were considered statistically significant if p value was below 0.05.

Results

At the University Hospital of Tours, 394 (18)F-Choline PET/CT were performed from 05/04/2013 to 25/04/2019 and 43 (68)Ga-PSMA PET/CT were performed from 17/05/2019 to 30/04/2021. At the end of the screening process, a total of 37 patients in the PSMA group and 36 patients in the Control group were included (*Figure 1*). In the PSMA group, 28 patients had sufficient follow-up data to be analyzed for the primary endpoint. These 28 patients were the ones taken into account for the comparative analysis of the two groups in order to limit bias.

1. Population description

Patients were initially diagnosed with localised prostate cancer between 2005 and 2020 in the PSMA group and between 1999 and 2016 in the Control group. Median age at diagnosis was 63.5 years old in the PSMA group and 61.6 years old in the Control group (p=0.15). Few patients were diagnosed with high grade tumors (ISUP score 4 or 5) but 71.4% and 66.7% of patients (p=0.83) had high risk of recurrence according to the D'Amico Risk Classification, in the PSMA and Control groups respectively (*Table 1*).

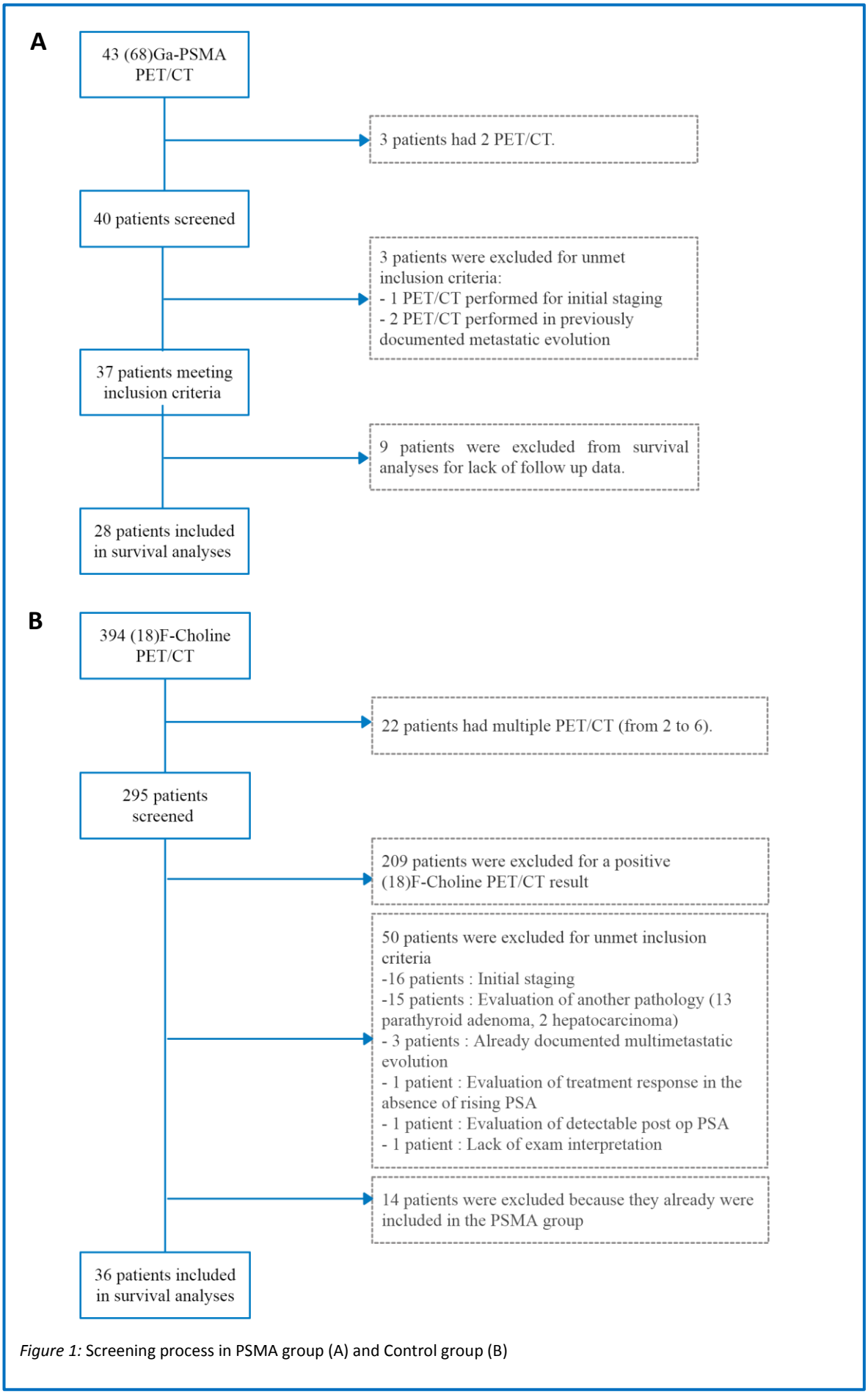


Figure 1: Screening process in PSMA group (A) and Control group (B)

Most patients were treated by radical prostatectomy: 67.9% and 72.2% of patients, in the PSMA and Control groups respectively (p=0.80). More than half of the patients received external pelvic radiotherapy: 57.1% and 63.9% of patients (p=0.49) with a median dose of 70 and 68 Gy delivered to the prostatic fossae, in the PSMA and Control groups respectively. Radiotherapy was administered in the adjuvant or salvage setting for about two third of the patients. Adjuvant ADT was given to 28.6% and 27.8% of patients (p=0.94), most patients had indication for a duration of 36 months but 80% and 66% stopped prematurely due to poor tolerance, in the PSMA and Control groups respectively. Four patients were treated with brachytherapy: two in the PSMA group and two in the Control group. One patient was treated with prostatic stereotactic radiotherapy in the Control group, and two patients in the PSMA group received neoadjuvant or adjuvant chemotherapy as part of clinical trials (*Table 2*).
Median PSA nadir after treatment was 0.35 ng/ml and 0.015 ng/ml (p=0.11) in the PSMA and Control groups respectively. Biochemical Recurrence (BCR) occurred after a median of 44.5 and 40.5 months (p=0.79) after local treatment, with a median PSA value of 2.64 and 1.69 ng/ml (p=0.33) and median PSA doubling time of 7.25 and 10 months (p=0.16), in the PSMA and Control groups respectively (*Table 3*).
No statistically significant difference was found between the two groups in terms of initial histoprognostic factors, initial therapeutic management nor BCR characteristics (*Tables 1 to 3*).

At the time of PET/CT, 35.7% and 55.5% of patients were presenting with rising PSA for the first time, 46.4% and 30.6% for the second time and had received one prior treatment, 14.3% and 5.6% for the third time and had received two types of prior treatment, in the PSMA and Control groups respectively (p=0.17).
Median PSA value before PET/CT was significantly higher in the PSMA group than in the Control group (3.33 ng/ml vs 2.57 ng/ml, p=0.02).

We analysed the localisation of hypermetabolic lesions detected by (68)Ga-PSMA PET/CT for the 37 patients included in the PSMA group. Patients had a median of two hypermetabolic lesions identified on PET/CT. No hypermetabolic lesion was found in 18.9% of patients, 45.9% had one to three lesions, 18.9% had four or five lesions and 16.2% had six lesions or more.

In our population, PSA value at (68)Ga-PSMA PET/CT was not correlated with the number of hypermetabolic lesion (Kendall' Tau-b= -0.11, p=0.45 and Spearman's rho= -0.14, p=0.48).

(68)Ga-PSMA PET/CT had a detection rate of 83.8%. It detected a local recurrence (in the prostatic fossae or seminal vesicles) for 13.5% of patients, a pelvic lymph node recurrence for 18.9%, an extra-pelvic lymph node recurrence for 21.6%, and a metastatic recurrence for 29.7% of patients (24.3% of bone metastases and 5.4% of visceral metastases) (*Table 4*).

After PET/CT, the treatment decision recorded in the medical file was more often in favour of active treatment in the PSMA group than in the Control group. Surveillance was chosen significantly less frequently in the PSMA group (25% vs 52.8% in the Control group, p=0.01).

Characteristics	PSMA (n = 28)	Control (n = 36)	p value
Age at diagnosis (years)			**0.15**
Median [min - max]	64 [51 - 76]	61 [52 - 74]	
Missing data	0	0	
PSA value at diagnosis (ng/ml)			**0.53**
Median [min - max]	8 [4.36 - 39]	8.77 [4.8 - 78]	
Missing data	3 (11%)	8 (22%)	
ISUP score			**0.16**
1	4 (14.3%)	11 (30.6%)	
2	9 (32.1%)	14 (38.9%)	
3	7 (25%)	4 (11.1%)	
4	4 (14.3%)	1 (2.8%)	
5	1 (3.6%)	2 (5.6%)	
Missing data	3 (10.7%)	4 (11.1%)	
Clinical stage			**0.81**
T1	1 (3.6%)	1 (2.8%)	
T2	11 (39.3%)	14 (38.9%)	
T3	12 (42.9%)	18 (50%)	
T4	1 (3.6%)	0	
Missing data	3 (10.7%)	3 (8.3%)	
Pelvic lymph node status			**0.48**
N0	24 (85.7%)	31 (86.1%)	
N+	3 (10.7%)	2 (5.6%)	
Missing data	1 (3.6%)	3 (8.3%)	
D'Amico Risk Classification			**0.83**
Low risk	0	1 (2.8%)	
Intermediate risk	6 (21.4%)	8 (22.2%)	
High risk	20 (71.4%)	24 (66.7%)	
Missing data	2 (7.1%)	3 (8.3%)	

Table 1 : Initial histoprognostic characteristics

Values are expressed as the number of patients and percentage, unless otherwise stated.

PSA: prostate-specific antigen ; ISUP: International Society of Urological Pathology

	PSMA (n = 28)	Control (n = 36)	p value
Local treatment			
Radical prostatectomy	**19 (67.9%)**	**26 (72.2%)**	**0.70**
Quality of resection (n = 19/26)			0.48
R0	9 (47.4%)	8 (30.7%)	
R1	7 (36.8%)	12 (46.2%)	
Missing data	3 (15.8%)	6 (23.1%)	
Radiotherapy to the prostatic fossae	**16 (57.1%)**	**23 (63.9%)**	**0.49**
Median dose delivered (Gy)	70	68	
Exclusive radiotherapy	7 (25%)	7 (19.4%)	
Adjuvant or early salvage radiotherapy	9 (32.1%)	16 (44.4%)	
Brachytherapy	**2 (7.1%)**	**2 (5.6%)**	**0.84**
Median dose delivered (Gy)	144	144	
Regional treatment			
Pelvic lymph node dissection	13 (46.4%)	19 (52.8%)	0.48
Pelvic radiotherapy	5 (17.9%)	3 (8.3%)	0.22
Median dose delivered (Gy)	46	46	
Adjuvant ADT	**8 (28.6%)**	**10 (27.8%)**	**0.94**
Median duration (months)	12	12.5	
6 months	1 (12.5%)	4 (40%)	
36 months completed	1 (12.5%)	2 (20%)	
36 months indicated but not completed	4 (50%)	4 (40%)	
Duration unknown	2 (25%)	0	
Other treatment	**2 (7.1%)***	**1 (2.8%) ****	**0.44**

Table 2 : Initial therapeutic management

*Neo or adjuvant chemotherapy in clinical trials **Prostatic stereotactic radiotherapy

Values are expressed as the number of patients and percentage, unless otherwise stated.

ADT : Androgen Deprivation Therapy

	PSMA (n = 28)	Control (n = 36)	p value
PSA nadir (ng/ml) after local treatment			**0.11**
Median [min - max]	0.35 [0 - 1.43]	0.015 [0 - 5.1]	
BCR characteristics			
Median PSA at BCR (ng/ml) [min - max]	2.64 [0.2 - 5.3]	1.69 [0.2 - 7.5]	0.33
Median time to BCR (months) [min - max]	44.5 [4 - 144]	40.5 [5 - 156]	0.79
Median PSA DT at BCR (months) [min - max]	7.25 [1 - 20]	10 [2 – 22]	0.16
Number of treatment lines after BCR			**0.17**
0	10 (35.7%)	20 (55.5%)	
1	13 (46.4%)	11 (30.6%)	
2	4 (14.3%)	2 (5.6%)	
Missing data	1 (3.6%)	3 (8.3%)	

Table 3 : Biochemical Recurrence (BCR)

Values are expressed as the number of patients and percentage, unless otherwise stated.

PSA: prostate-specific antigen; BCR: BioChemical Recurrence; PSA DT: PSA doubling time

A higher rate of patients was treated with radiotherapy in the PSMA group (35.7% vs 13.9% in the Control group), however the difference was not found to be statistically significant (p=0.06). A significantly higher rate of patient was treated with ADT in the PSMA group (50% vs 22.2% in the Control group, p=0.03). One patient was treated with brachytherapy in the PSMA group, no patient was treated with surgery.

	PSMA (n = 37)
No recurrence site identified	**6 (16.2%)**
Local recurrence	**5 (13.5%)**
Lymph node recurrence	**15 (40.5%)**
Pelvic	7 (18.9%)
Extra pelvic	8 (21.6%)
Metastatic recurrence	**11 (29.7%)**
Bone metastasis	9 (24.3%)
Viscera	2 (5.4%)

Table 4: Localisation of hypermetabolic lesions on (68)-Ga PSMA PET/CT
When recurrence was detected at multiple sites, patients were assigned into the category associated with the worse prognosis.

2. Changes of therapeutic proposition resulting from (68)Ga-PSMA PET/CT

(68)Ga-PSMA PET/CT results induced changes in therapeutic proposition of a multidisciplinary staff meeting for 22 out of the 28 patients (79%). (*Figure 2*)

(68)Ga-PSMA PET/CT results led to the following changes:

- Active treatment instead of surveillance for 18 patients (64%)
  - Radiotherapy for 12 patients (43%), including stereotactic radiotherapy for 8 patients (29%)
  - ADT for 6 patients (21%)
- Delayed introduction of ADT for 3 patients (11%) in favour of:
  - Surveillance for 2 patients
  - Radiotherapy for 1 patient
- Abandonment of radiotherapy and introduction of ADT for 1 patient (4%)

Treatment was not modified by the (68)Ga-PSMA PET/CT results for six patients (21%) and patients received :

- ADT for 3 patients (11%)
- Surveillance for 3 patients (11%)

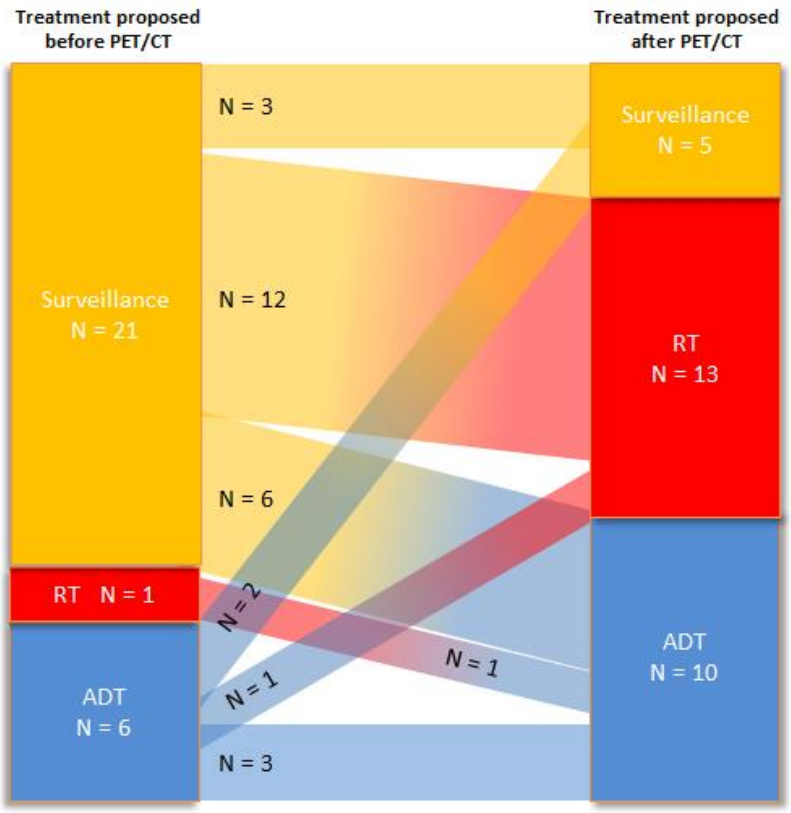


Figure 2: Changes in treatment decision after (68)Ga-PSMA PET/CT
ADT: Androgen Deprivation Therapy; RT: Radiotherapy

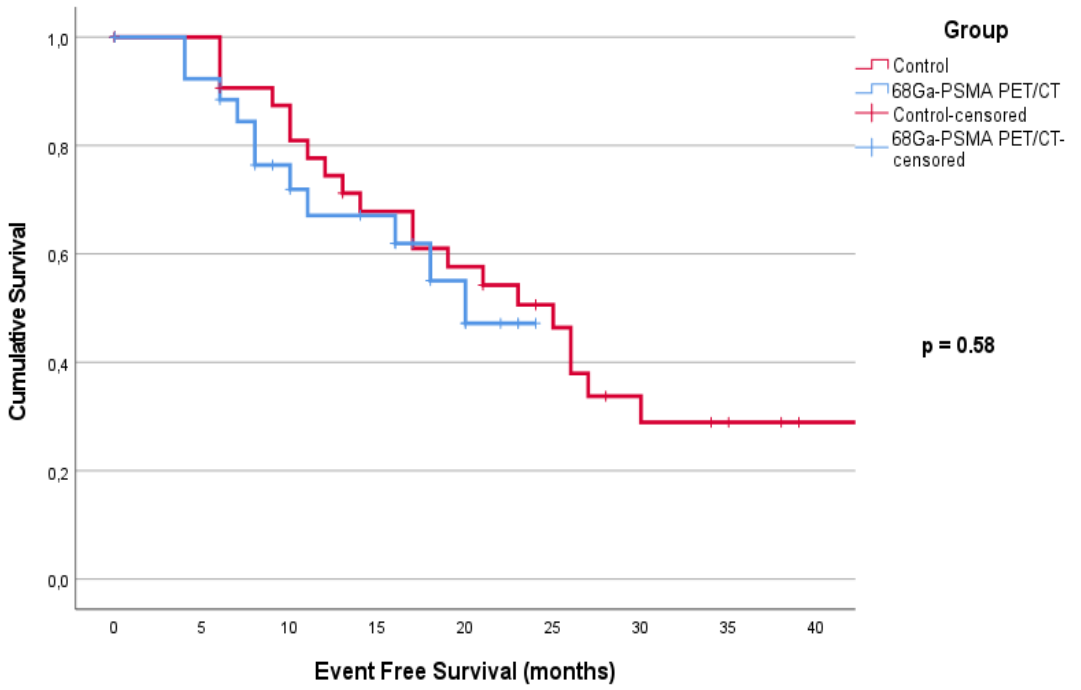
3. Survival endpoints

The clinical data cut-off date for survival analyses was June 22, 2021. Median follow up was 16 months in the PSMA group versus 37.5 months in the Control group (p<0.001).

Event Free Survival (EFS) was not statistically different between the two groups (p=0.58) with a median of 20 and 25 months, in the PSMA and Control group respectively (*Figure 3*). We recorded 11 events in the PSMA group and 20 events in the Control group.
When stratified according to the treatment received after PET/CT (regardless of the radiotracer used), disease control appeared to be similar whether patients received ADT or radiotherapy with a median EFS not reached in both groups (p=0.79) (*Figure 4*).

ADT Free Survival was significantly shorter in the PSMA group with a median of 10 months versus 35 months in the Control group (p=0.003), which means ADT was introduced earlier when patients underwent (68)Ga-PSMA PET/CT (*Figure 5*).
Ten patients were censored because they were already receiving ADT at the time of the PET/CT (4 in the PSMA group, 6 in the Control group).

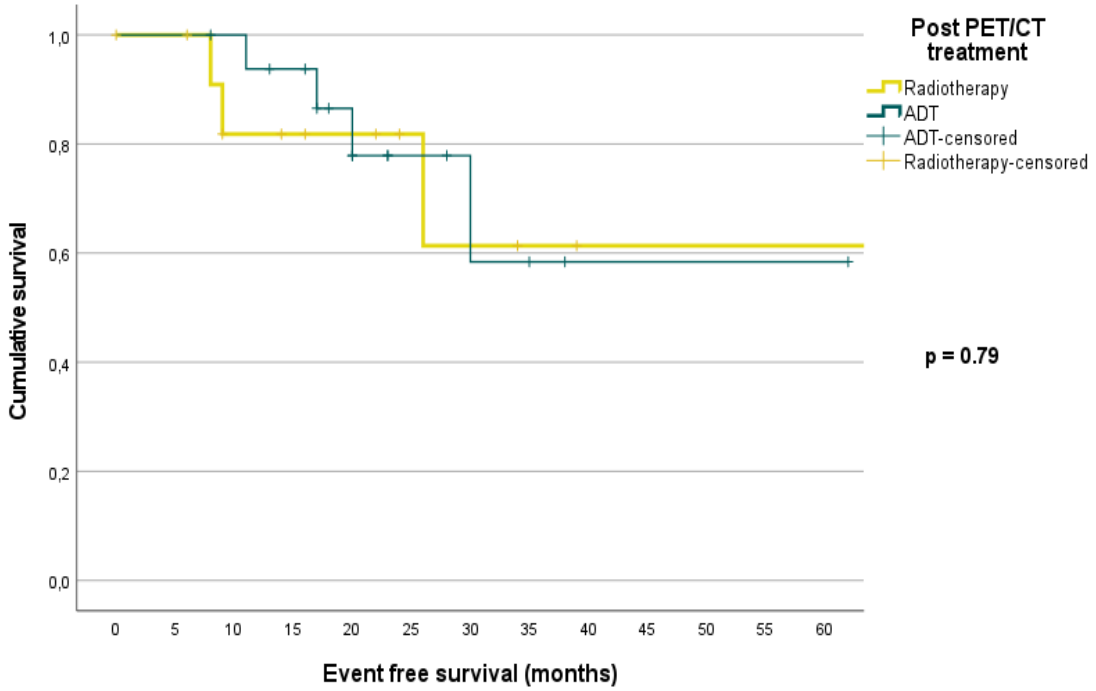
Overall Survival was not interpretable due to the limited number of event. No patient died in the PSMA group, one patient died in the control group as a result of cancer evolution.



Number at risk (number censored)

PSMA	28	24	15	13	4	0	0	0	0
	(0)	(2)	(5)	(7)	(11)	(17)	(17)	(17)	(17)
Control	36	32	25	20	17	11	6	4	2
	(0)	(4)	(5)	(6)	(6)	(9)	(10)	(11)	(14)

Figure 3: Primary Endpoint: Event Free Survival (PSA progression and/or change of therapeutic line)

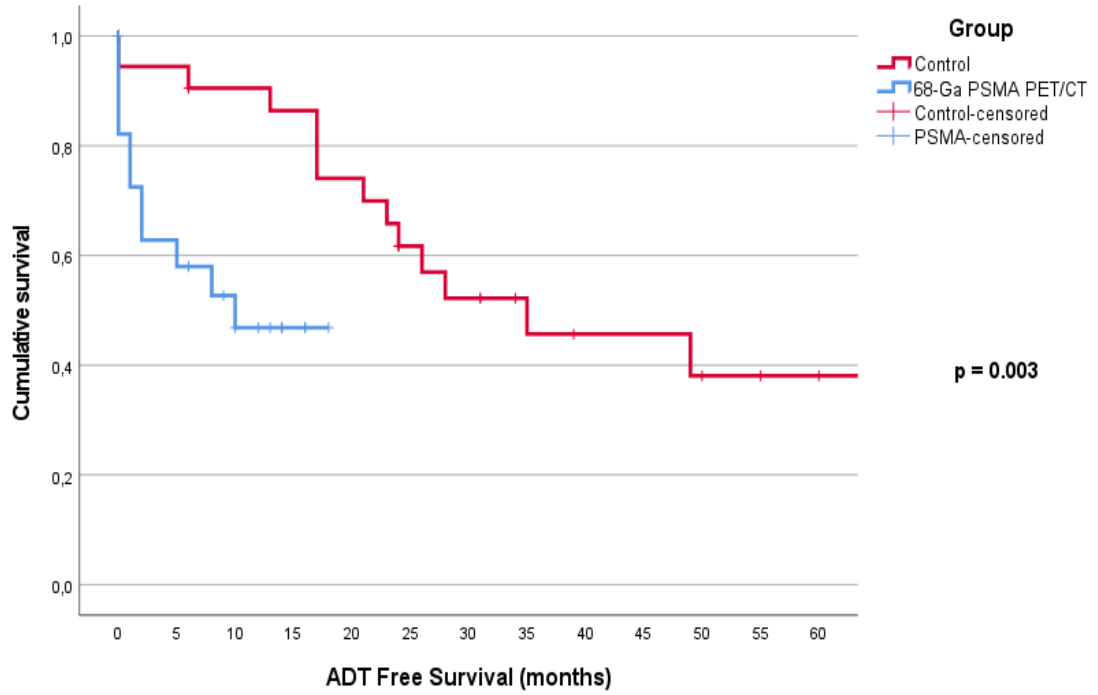


Number at risk (number censored)

ADT	17	17	16	14	7	5	3	2	1	1	1	1	1
	(0)	(0)	(1)	(2)	(5)	(9)	(10)	(10)	(12)	(12)	(12)	(12)	(12)
RT	13	12	8	7	6	4	3	2	1	1	1	1	1
	(0)	(1)	(3)	(4)	(5)	(7)	(7)	(8)	(9)	(9)	(9)	(9)	(9)

Figure 4: Event Free Survival stratified by treatment received after PET/CT

ADT: Androgen Derivation Therapy; RT: Radiotherapy



Number at risk (number censored)

PSMA	28 (6)	12 (6)	7 (8)	3 (13)	0 (16)	0 (16)	0 (16)	0 (16)	0 (16)	0 (16)	0 (16)	0 (16)	0 (16)
Control	36 (4)	24 (10)	22 (11)	21 (11)	18 (11)	13 (13)	11 (13)	7 (16)	6 (17)	6 (17)	4 (17)	3 (18)	2 (19)

Figure 5: Androgen Deprivation Therapy Free Survival
ADT: Androgen Derivation Therapy

4. PSA response rate

PSA response rate, defined as any PSA response, was higher in the PSMA group with a rate of 60.7% versus 41.7% in the Control group, but statistical significance was not reached (p=0.31). When analysing best PSA response, we observed a higher proportion of major partial response (defined as a PSA decrease over 50%) in the PSMA group (52.9% vs 30.8% in the Control group) and a lower proportion of progressive disease (28.6% vs 44.4% in the Control group) (*Table 5*).

	PSMA (n = 28)	Control (n = 36)	p value
PSA response	**17 (60.7%)**	**15 (41.7%)**	**0.31**
Best PSA response			**0.14**
Complete Response (CR)	4 (14.3%)	5 (13.9%)	
Major Partial Response (MPR)	11 (39.3%)	4 (11.1%)	
Partial Response (PR)	1 (3.6%)	1 (2.8%)	
Stable Disease (SD)	1 (3.6%)	5 (13.9%)	
Progressive Disease (PD)	8 (28.6%)	16 (44.4%)	
Non Assessable (NA)	3 (10.7%)	5 (13.9%)	

Table 5: PSA response characteristics
PSA Response was defined as any kind of PSA response including stability
Progressive Disease: PSA increase of at least 25%; Major partial response: PSA decrease of more than 50%; Complete response: undetectable PSA

Discussion

With a detection rate of about 78% at PSA levels between 1 and 2 ng/ml and 93% over 2 ng/ml, (68)Ga-PSMA PET/CT has proved in numerous publications to be more sensitive for restaging for rising PSA than Technetium Bone Scan or even (18)F-Choline PET/CT especially for low PSA levels (5,9,10).

In our study, performances of (68)Ga-PSMA PET/CT were a little lower. Detection rate was 84%, revealing at least one target lesion in 31 out of 37 patients, with a median PSA level of 3.3 ng/ml at the time of the exam. These performances are still satisfactory and are particularly noteworthy considering that, in our study, the exam was conducted into a subpopulation of patients who had a prior negative (18)F-Choline PET/CT whereas most of the studies on (68)Ga-PSMA PET/CT performances considered all patients with rising PSA with no requirement of prior negative (18)F-Choline PET/CT.

In a population of patients with prior negative (18)F-Choline PET/CT, detection rate was 43% in Bluemel *et al*.'s cohort with a median PSA of 1.96 ng/ml, 76% in Gauthé *et al*.'s cohort with a median PSA of 2.8 ng/ml and 81% in Barbaud *et al*.'s cohort with a median PSA of 2.6 ng/ml (11–13).

In our study, (68)Ga-PSMA PET/CT led to changes in planned cancer management for more than 3 patients out of 4 (79%). In a meta-analysis, Han *et al*. reported changes in management for 29% to 77% of patients with a pooled proportion of change of 54% (8). They included 15 studies: four studies included patients undergoing PET/CT for initial staging, six studies only included patients considered for salvage radiotherapy at BCR and five studies considered patients experiencing a rising PSA regardless of the treatment proposition before PET/CT. In this meta-analysis, after (68)Ga-PSMA PET/CT, there was an increasing proportion of local treatment (radiotherapy increased from 56% to 61% and surgery increased from 1% to 7%) and a decreasing proportion of ADT (from 26% to 12%) and surveillance (from 14% to 11%). In our study, we also observed a higher proportion of radiotherapy after (68)Ga-PSMA PET/CT, indications rising from 4% to 46%. The much higher rate of radiotherapy indication before PET/CT in the meta-analysis is explained by the six studies that only included patients for whom a salvage pelvic radiotherapy was considered before PET/CT. In our study, most patients were not eligible for salvage pelvic radiotherapy, as 23 patients (82%) had already received pelvic radiotherapy at the time of PET/CT (initial exclusive radiotherapy, adjuvant or salvage radiotherapy).

Concerning ADT indications, we did not observe a decrease after PET/CT but a rise from 21% to 36% as we probably considered patients with more advanced and pre-treated diseases. Median PSA level at (68)Ga-PSMA PET/CT was higher than in most studies as its realization was conditioned by a prior negative (18)F-Choline PET/CT which is usually performed at PSA level of 2 ng/ml or above. A higher PSA value at the time of PET/CT has been correlated with higher metabolic tumour volume (15–17). In our population, statistical correlation between PSA level and the number of hypermetabolic lesion detected was not demonstrated. However, when compared with Perera *et al.*'s meta-analysis including 37 articles, the relapses detected by (68)Ga-PSMA PET/CT in our study were at more advanced stages. We observed an under-representation of local recurrence detected on (68)Ga-PSMA PET/CT (16% of patients with a positive PET scan versus 28% in the meta-analysis) and pelvic

recurrence (23% vs 38%) and an over-representation of extrapelvic lymph node recurrence (26% vs 13%) and metastatic recurrence (35% vs 27%) (14). Furthermore, half of the patients in the PSMA group and a third in the Control group had received one or two previous treatments for rising PSA before PET/CT.

This opens up the debate about optimal timing of (68)Ga-PSMA PET/CT and the relevance of current French ATU requirement of a prior negative (18)F-Choline PET/CT. Should (68)Ga-PSMA PET/CT be performed sooner into the course of patient's history to benefit from the best performances and detect relapses at earlier stages? Should we skip (18)F-Choline PET/CT altogether and perform first line (68)Ga-PSMA PET/CT when patients present with rising PSA?
We could be tempted to consider it, as multiplying exam modalities can be tedious and time consuming, but expanding indications for (68)Ga-PSMA PET/CT also implies logistical difficulties to produce 68-Gallium in large quantity and an increasing economic cost.
As the half-life of 68-Gallium is too short to allow transport from a production site using a cyclotron, it requires an on-site production with a generator. 68-Gallium generators have a low output and, for example, we can only perform one (68)Ga-PSMA PET/CT per week at the University Hospital of Tours. Ongoing development of 18-Fluor radiolabeled PSMA ligands and nomograms improving selection of patients with better chances of positive results could help to overcome this problem(18–20).

To justify development of (68)Ga-PSMA PET/CT, we should first assess its clinical impact. For now, it is still unclear whether changes in clinical practice resulting from (68)Ga-PSMA PET/CT are really improving clinical outcomes compared to practices based on (18)F-Choline PET/CT. To our knowledge, ours is one of the first comparative studies considering this question in a real world population. However, there was no statistical difference in Event Free Survival (p=0.58). It could be partially due to our limited population size and follow up. Data were especially immature in the PSMA group as the median follow up was only 16 months, with events occurring after a median of 20 months. Another limitation of our study is the questionable relevance of this composite endpoint including PSA control which is a controversial surrogate for survival, yet it is widely used in similar studies due to the need of years of follow up to obtain survival data in rising PSA in prostate cancer (21).
Fourquet *et al*.'s study demonstrated a good efficacy of treatments guided by (68)Ga-PSMA PET/CT with an overall PSA response rate of 78% but did not provide a comparative arm or survival analyses to assess the duration of the response (22).

Most of the published trials focus on oligometastatic prostate cancer recurrence detected after PET/CT, excluding patients ineligible to loco-regional treatment. The definition of oligometastatic recurrence is yet to be formalised (1 to 3 or 5 metastases in most studies) and this entity is thought to be at the frontier between locally confined and more disseminated disease, with an intermediate prognosis. Those trials are testing locoregional treatments efficacy, mainly radiotherapy, guided by nuclear imaging in oligometastatic situation. The goal is to delay systemic treatment and perhaps even pretend to a curative intent, or at least to improve overall survival.

Studies show an interesting local control efficacy of radiotherapy directed at lesions detected by the PET/CT, also called Metastasis Directed Therapy (MDT), and international guidelines already consider it to be an option (3,23,24).
Mazzola *et al.* conducted a retrospective study comparing the efficacy of stereotactic body radiotherapy (SBRT) guided by (18)F-Choline PET/CT versus (68)Ga-PSMA PET/CT in oligometastatic relapses (25). The study included 88 patients with an equal distribution in the two cohorts. Most of the lesions treated were lymph node metastases. Distant Progression Free-Survival (dPFS) following SBRT, defined as recurrence detected outside the SBRT fields, was not significantly different in both groups, with a median overall dPFS of 23 months. ADT Free Survival was significantly prolonged by SBRT guided by (68)Ga-PSMA PET/CT (p=0.01).
Deijen *et al.* conducted a similar study on a 50 patients cohort exhibiting oligometastatic recurrence (up to four metastases, with a majority of lymph node lesions) (26). PSMA PET/CT guided SBRT resulted in longer PSA response (median of 34.0 months versus 14.7 months, p=0.004) and ADT Free Survival (median of 32.7 months versus 14.9 months, p=0.01) compared to Choline PET/CT guided SBRT.
In smaller cohorts, time to PSA progression after (68)Ga-PSMA PET/CT guided radiotherapy for lymph node metastases and bone metastases was respectively 16 and 7 months(27,28).

Optimal management of oligometastatic relapse is not consensual, as some are defending immediate ADT, arguing that, even if new imaging tests are more sensitive, oligometastatic lesions are still the tip of the iceberg and we underestimate the extent of the disease. Differing ADT in favour of MDT could then be suboptimal as cancer has already spread outside of the lesions treated. In our study, when stratified on the treatment chosen after PET/CT, regardless of the type of PET/CT, ADT and radiotherapy showed similar PSA control. Others may argue that MDT could delay the time to castration resistance or modify the natural history of the castration-sensitive prostate cancer. Expert consensus currently recommends combining MDT with ADT(29).

(68)Ga-PSMA PET/CT interest is not limited to the diagnosis of oligometastatic diseases and it also impacts treatment management through early detection of multimetastatic evolution. In our study, 36% of the patients had at least four hypermetabolic lesions, indicative of a disseminated stage with little or no possibility of a locoregional treatment. This resulted in a significantly earlier introduction of ADT in the PSMA group compared to the Control group.

The right timing to initiate ADT for a rising PSA is still a controversial issue and the medical community is divided. ADT has proven its efficacy on PSA response but is also responsible for an increased risk of cardiovascular disease, metabolic complications, cognitive decline and sexual dysfunction. Therefore, practitioners are often reluctant to start ADT at low PSA levels to avoid its toxicity and impact on quality of life when there is no target lesion identified on imaging exams.
In a review published in 2015, including two randomised trials and mostly non randomised studies and case series, there was no clear survival benefit of early ADT for rising PSA (30).
For now, guidelines tend to recommend early ADT for patients with a short PSA doubling time as they consider this parameter to be a surrogate of tumor aggressiveness (3).

In *de novo* metastatic prostate cancer identified with traditional imaging, early ADT has become the standard of care with data indicating probable increased overall and cancer-specific survival and decreased skeletal events compared with delayed ADT(31,32). The trend is even towards therapeutic escalation as trials demonstrated better OS when ADT is associated with Abiraterone, Enzalutamide, Apalutamide or Docetaxel for castration-naïve prostate cancer(33–38). As these studies included mostly patients diagnosed with *de novo* metastatic cancer, we do not know, however, if these data can be extrapolated to metachronous metastatic relapses.

Conclusion

This study is one of the first comparative studies trying to assess clinical benefit of a treatment strategy based on (68)Ga-PSMA PET/CT after a negative or inconclusive (18)F-Choline PET/CT. The most frequent change in clinical management resulting from (68)Ga-PSMA PET/CT was to start an active treatment, Metastasis Directed Radiotherapy (MDT) or earlier onset of Androgen Deprivation Therapy (ADT), instead of going on with surveillance. However, we found no clinical benefit of this treatment strategy. Data from the literature has shown that MDT is a feasible option but long-term clinical benefits are still unknown. Early ADT in *de novo* metastatic setting is the standard of care but we lack information concerning metachronous metastatic relapses detected with PET/CT. Further prospective studies with larger population size and longer follow-up are needed to confirm these results.

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Vu, le Directeur de Thèse

CENTRE REGIONAL DE CANCEROLOGIE
Service d'Oncologie Médicale
Pr LINASSIER
Hôpital Bretonneau - 37044 TOURS CEDEX 9
Secrétariat : 02 47 47 99 19
Fax : 02 47 47 99 20
Poste infirmier : 02 47 47 80 13

Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

académie d'Orléans-Tours | université de TOURS | Faculté de médecine

LEGER Cécilia

34 pages – 5 tableaux – 5 figures

Résumé :
La prise en charge de la réascension du PSA, après un traitement local à but curatif du cancer de prostate, a beaucoup évolué avec l'arrivée des techniques d'imagerie nucléaire permettant une meilleure détection de la localisation des récidives. Cependant, l'impact clinique à long terme des décisions de traitement en résultant reste à déterminer.
L'objectif de cette étude est d'évaluer le bénéfice d'une stratégie de traitement basée sur les résultats de la TEP-TDM (68)Ga-PSMA après une TEP-TDM (18)F-Choline négative.
Nous avons mené une étude rétrospective cas-témoins. Nous avons inclus 28 patients ayant bénéficié d'une TEP-TDM au (68)Ga-PSMA pour une réascension des PSA dans le cadre de l'ATU et, dans le groupe contrôle, 36 patients traités avant l'arrivée de la TEP-TDM au (68)Ga-PSMA, qui avaient eu une TEP-TDM au (18)F-Choline négative lors de la réascension du PSA.
Les résultats de la TEP-TDM au (68)Ga-PSMA ont modifié la décision thérapeutique pour 79% des patients. Le changement le plus fréquent était de débuter un traitement actif (radiothérapie pour 2/3 des patients et hormonothérapie pour 1/3 des patients) au lieu de poursuivre la surveillance. Le critère de jugement principal était la survie sans événement, définie comme l'intervalle de temps entre la TEP-TDM et la progression du PSA et/ou le changement de ligne de traitement. Celle-ci n'était pas statistiquement différente entre les deux groupes (p=0,58). La survie sans hormonothérapie était significativement plus courte dans le groupe PSMA (médiane de 10 mois contre 35 mois dans le groupe témoin, p=0,003). Le taux de réponse des PSA était de 60,7% dans le groupe PSMA contre 41,7% dans le groupe contrôle (p=0,31).
La TEP-TDM au (68)Ga-PSMA a induit un changement de traitement pour la majorité des patients, mais notre étude ne met pas en évidence de bénéfice clinique de la stratégie de traitement en résultant. Des études ayant un effectif plus important et un suivi plus long sont nécessaires.

Mots clés : Cancer de Prostate - Récidive biochimique - Ascension du PSA - TEP-TDM au (68)Ga-PSMA - TEP-TDM au (18)F-Choline

Jury :

Président du Jury :	Professeur Claude LINASSIER
Directeur de thèse :	Docteur Mathilde CANCEL
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	Professeur Gilles CALAIS
	Docteur Bérengère NARCISO

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