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ORIGINAL PAPER

Accuracy of PET-choline in nodal staging of localized very high-risk prostate cancer

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Summary ***Objectives: Localized very high-risk prostate cancer (VHR PCa) has long suffered from the inex-istence of good lymph node staging methods other than invasive surgery, as computed tomogra-phy has low sensitivity for nodal disease. With the rising use of positron emission tomography (PET), it is clinically meaningful to know its value for these patients. Our goal was to evaluate the real-life diagnostic accuracy of PET Choline in nodal staging, comparing it with the gold standard of extended pelvic lymph node dissection (ePLND).***

Materials and methods: We reviewed data from a high-volume center, including patients with VHR PCa according to current NCCN guidelines who underwent community 18F-fluorocholine PET/CT; followed by ro-botic assisted laparoscopic prostatectomy (RALP) and ePLND between 2010 and 2021.

Results: We included 44 patients and 88 lymph node regions. Among those, 14/44 (31.8%) patients and 20/88 (22.7%) regions had nodal disease present on definitive pathology.

In comparison with ePLND, we found a sensitivity of 64.3% (95% CI, 39.2-89.4%), specificity of 83.3% (95% CI, 70.0-96.7%), PPV of 64.3% (95% CI, 39.2-89.4%), and NPV of 83.3% (95% CI, 70.0-96.7%) for nodal disease on a patient-based analysis; and sensitivity of 35.0% (95% CI, 14.1-60.0%), specificity of 88.2% (95% CI, 80.6-95.9%), PPV of 46.7% (95% CI, 21.4-71.9%), and NPV of 82.2% (95% CI, 73.4-91.0%) on a region-based analysis.

Conclusions: In our view 18F-fluorocholine PET/CT doesn't meet the criteria to be a standard exam for pre-operative staging for patients with VHR PCa, mostly due to its low sensitivity. However, other radiotracers should continue to be investigated in this setting.

KEY WORDS: Positron-emission tomography; Prostatic neoplasms; Neoplasm staging.

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INTRODUCTION

Adequately staging of *very high-risk* (VHR) localized *prostate cancer* (PCa) is of utmost importance, as staging may alter treatment choice. Even when patients are well selected for radical treatment, their biochemical recurrence, metastasis, cancer specific mortality and all-cause mortality at 5 years can be as high as 69%, 20%, 5% and 7%, respectively (1, 2). After the diagnosis, a better staging would allow both clinician and patient a better-informed choice and a better tailored treatment approach. Current recommendations from *European Association of Urology* (EAU) (3) and *National Comprehensive Cancer Network* (NCCN) (4) are for high-risk and VHR localized PCa patients to undergo *computed tomography* (CT) of abdomen and pelvis and whole-body bone scan (BSc). However, it is commonly known that CT and alternatives such as *Magnetic Resonance Imaging* (MRI) have a modest performance for nodal staging (5).

More recent nuclear imaging such as *Positron Emission Tomography* (PET) with Choline or *Prostate-Specific Membrane Antigen* (PSMA) isotopes have been explored, but their utilization in staging localized PCa is not standard (6, 7). PET-PSMA is currently regarded as the most promising radiotracer, but in most of the world it is more expensive and of more limited availability than PET-Choline (8). As such, in France, it is frequent that we find patients being staged with PET-Choline, exam considered in guidelines as having a role in biochemical recurrence. It has the advantage of being cheaper, easily available and reproducible (8). However, its role in staging of localized PCa is disputed, with some papers reporting interesting results in the subset of high risk and VHR patients (9, 10). In this work we explore the role of PET Choline realized in community non-centralized centers in node staging, when compared with CT findings and with the gold standard of bilateral extended pelvic lymphadenectomy, in patients with VHR PCa.

METHODS

Our center is a high-ranking hospital in PCa care, receiving patients mainly from Paris, but also from all France and the rest of the World. We maintain a prospectively updated database with all patients who undergo a radical prostatectomy in our center, including our study population. We explored this database for patients with VHR localized PCa who underwent PET Choline as a method of pre-operative staging, who were treated with *Robotic Assisted Laparoscopic Prostatectomy* (RALP) and *Extended Pelvic Lymph Node Dissection* (ePLND), between 2010 and

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2021. Patients who had a previous malignancy or history of prior hormonal therapy were excluded.

Data collection

Data was collected from our continuously updated database and patient records. We recorded age at time of surgery, pre-operative total PSA, clinical T staging, biopsy results, PET Choline results, anatomopathological study of prostatectomy and lymph node dissection specimens. The study has received approval by the institutional Ethics' Committee. All research was conducted respecting the latest version of Helsinki's declaration.

Risk groups

Patients were included if they fulfilled current NCCN guidelines (4) criteria for VHR patients: a) at least 1 of: cT3b-cT4, primary Gleason pattern 5, > 4 cores with Gleason Group 4 or 5; and/or b) at least 2 of: cT3a, Gleason Group 4 or 5, PSA > 20 ng/mL.

PET Choline

PET/CT exams were performed in various local centers in France, with images acquired using ^{18}F-fluorocholine tracer being obtained according to institutional protocols, with images being reported by several different community radiologists. PET Choline imaging were acquired alongside a tho-raco-abdominal-pelvic CT scan. Images were not centrally reviewed.

The diagnosis of pathological lymph nodes was based on the presence of increased uptake on PET images of the radiotracer, with exams being considered as positive if reported by the radiologist as positive or suspicious, irrespective of standardized uptake value (SUV). CT adjunctive imaging was used only to locate the anomalies and not as a staging method by itself.

Surgery

RALP + ePLND was performed in our institution by seven different assistants, with long experience in robotic surgery and RALP, with frequent participation of fellows under their direct supervi-sion. RALP was performed transperitoneally, and ePLND was performed as per guidelines standard (including node packets from common iliac distal to the ureteric crossing, external iliac, internal iliac, and obturator origins), with nodes from each side being sent and analyzed separately (3). Other nodal regions such as presacral and retroperitoneal would only be removed in select cases where imaging was suspicious of lymph node metastasis in those locations, with no cases present in our population.

Histology

Biopsy cores were analyzed in the institution where the biopsy was performed and not reviewed, except in doubtful cases. Prostatectomy and lymph node dissection products were fixed in formalin and examined in our center by specialized uropathologists, in accordance with ISUP guidelines, with left and right templates being observed separately (11).

Statistics

Statistical analysis was performed with IBM® SPSS® v27 software. Median and interquartile range are presented for continuous variables; frequencies are reported for categorical variables. Characteristics of patients were compared using Chi-squared analysis for categorical variables and non-parametric Mann-Whitney U tests for continuous variables (age). Statistically significance in this study was set as $p < 0.05$. All reported p values are two-sided. Test characteristics (sensitivity, specificity, VPP, VPN) were calculated for both patient and region based analysis, with 95% confidence intervals.

Results

We identified 2104 consecutive patients submitted to RALP, with 104 being VHR patients and 45 who had had PET Choline as part of their disease staging. One patient meeting the inclusion criteria was excluded for not having all information regarding PET Choline examen available. Forty-four patients and eighty-eight lymph node regions were included in our analysis.

Patient characteristics

Patient characteristics are shown in Table 1. Median patient age was of 63 years old (IQR 59-68) and median total PSA of 15 (IQR 9.8-22.2) ng/mL, with 23 patients having a PSA > 15 ng/mL. All 44 patients had VHR PCa,

Table 1.
Patient characteristics.

	Total n = 44
Age, median (P25-P75)	63 (59-68)
Total PSA, ng/mL, median (P25-75)	15 (9.8-22.2)
Clinical T stage, n (%)	
T1c	4 (9)
T2a	6 (14)
T2b	4 (9)
T2c	8 (18)
T3a	17 (39)
T3b	5 (11)
Biopsy at our institution	15 (34)
Biopsy ISUP, n (%)	
1	5 (11)
2	6 (14)
3	8 (18)
4	16 (36)
5	9 (21)
Number positive cores, median (P25-75)	6 (4-7)
> 4 cores with ISUP ≥ 4, n (%)	17 (39)
Pathological T stage, n (%)	
T2b	1 (2)
T2c	7 (16)
T3a	21 (48)
T3b	15 (34)
Prostatectomy ISUP, n (%)	
2	8 (18)
3	22 (50)
4	4 (9)
5	10 (23)
Nodal disease, n (%)	14 (32)
Number of positive lymph-nodes, n (%)	
0	30 (68)
1	4 (9)
2	1 (2)
≥ 3	9 (20)
Number removed nodes, median (P25-75)	19 (11-26)

Table 2.
Two-by-two tables presenting cross-results for nodal disease of ePLND and ^{18}F PET-Choline, on patient and region-based analysis.

^{18}F PET-Choline	Positive ePLND	Negative ePLND
Patient-based analysis		
Total, n	14	30
Positive/suspicious, n (%)	9 (64)	5 (17)
Negative, n (%)	5 (36)	25 (83)
Region-based analysis		
Total, n	20	68
Positive/suspicious, n (%)	7 (35)	8 (12)
Negative, n (%)	13 (65)	60 (88)

with 17 (39%) and 5 (11%) having cT3a and cT3b disease, respectively. Overall, 9 (21%) patients had ISUP of 5, and 17 (39%) had more than 4 biopsy cores with ISUP ≥ 4. Histological results after RALP + ePLND showed most patients locally advanced disease, with 48% presenting with pT3a and 34% with pT3b disease; and 23% of patients had a Gleason Grade Group of 5. With a median 19 (IQR 11-26) nodes removed per patient, 14 out of 44 (32%) of patients had nodal metastasis. Four (9%) patients had 1 positive lymph node, 1 (2%) had 2 positive lymph nodes and 9 (20%) had ≥ 3 positive lymph nodes identified.

^{18}F-fluorocholine PET/CT and ePLND

Table 2 presents the cross results between ^{18}F-fluorocholine PET/CT and anatomopathological findings, in a patient and region base analysis. When compared with ePLND, ^{18}F-fluorocholine PET/CT had a false negative rate of 17% and 18% for patient and region-based analysis, respectively; and a false positive rate of 50% and 53%, respectively.

Table 3 shows the performance of ^{18}F-fluorocholine PET/CT as a test for nodal staging. On a patient-based analysis (n=44); sensitivity was 64.3% (95% CI, 39.2-89.4%), specificity 83.3% (95% CI, 70.0-96.7%), PPV 64.3% (95% CI, 39.2-89.4%), and NPV 83.3% (95% CI, 70.0-96.7%). On a region-based analysis (n=88); sensitivity was 35.0% (95% CI, 14.1-56.0%), specificity 88.2% (95% CI, 80.6-95.9%), PPV 46.7% (95% CI, 21.4-71.9%), and NPV 82.2% (95% CI, 73.4-91.0%). Knowing the correlation between biomarkers uptake and PSA, we performed the same analysis for patients with PSA > 15ng/mL and on a region basis; sensitivity was 50% (95% CI, 24-76%), with specificity of 84% (95% CI, 72-97%), PPV of 58% (95% CI, 30-86%) and NPV of 79% (95% CI, 66-93%).

Table 3.
Test performance on patient and region-based analysis.

^{18}F PET-Choline	Values
Patient-based analysis	
Patients with positive LN	14/44 (31.8%)
Sensitivity	64.3% [39.2-89.4%]
Specificity	83.3% [70.0-96.7%]
PPV	64.3% [39.2-89.4%]
NPV	83.3% [70.0-96.7%]
Region-based analysis	
Regions with positive LN	20/88 (22.7%)
Sensitivity	35.0% [14.1-56.0%]
Specificity	88.2% [80.6-95.9%]
PPV	46.7% [21.4-71.9%]
NPV	82.2% [73.4-91.0%]

Sub-group with ≥ 3 positive lymph nodes

Nine (20%) patients had at least 3 positive lymph nodes at final pathology, with 6 of them having a positive ^{18}F-fluorocholine PET/CT. For this subgroup, on a patient-based analysis (n=9); sensitivity was 66.7% (95% CI, 35.9-97.5%), specificity 77.1% (95% CI, 63.2-91.1%), PPV 42.9% (95% CI, 16.9-68.8%), and NPV 90.0% (95% CI, 79.3-100.0%).

Discussion

The importance of a good nodal staging in VHR PCa patients is three ways. First, patients with node positive disease should be well identified, since these patients may benefit from adjuvant hormonal therapy and/or radiotherapy after surgery, and because they have worse outcomes in biochemical free survival, metastasis free survival and overall survival (2). Second, when discussing treatment options with a patient before deciding on a radical treatment, we should be able to provide him with the best information possible, in order to allow the best individual decision. In VHR patients in particular, the rate of node positive disease has been estimated to be as high as 37% (2). Third, when surgery for VHR patients is performed, it entails not only radical prostatectomy but also an ePLND, which increases surgical time and risk of perioperative complications, and has not been shown to lead to better patient outcomes (12).

As such, if an accurate enough non-invasive staging method were easily available, it could lead to better identifications of node positive patients before intervention, best individualized information before treatment decisions and eventual nonrealization of a procedure with significant comorbidities but no increased benefit to patients (12).

Current recommended staging of localized VHR PCa is CT and whole-body bone scan (3, 4). CT scan relies mainly on size criteria, location and contrast enhancement to classify lymph nodes as suspicious or not. However, CT scan has been extensively reported as having a poor performance for nodal staging, with sensitivity depending on the prostate cancer risk, but remaining low even for high-risk patients (13). Knowing this, previous studies have searched for adequate methods for non-invasive PCa staging. Those alternatives should be sensitive, specific, clinically useful, easily accessible and reproducible (14). Previous studies have explored the role of PET Choline and PET PSMA as staging imaging for localized PCa, mostly in a trial setting.

Van den Bergh et al. (9) performed a prospective study with 75 patients with negative CT scans and lymph node extension risk assessed to be between 10-35% with Partin tables and compared the performance of pre-operative staging with 11C-Choline PET and pelvic MRI with super-extended pelvic lymphadenectomy results. They reported a low performance of both PET and MRI, main-

ly at the expenses of a low sensitivity (PET: 19% and 8% on patient and region-based analysis; MRI: 36% and 10% on patient and region-based analysis), which lead them to suggest the absence of benefit in this patient cohort.
Schiavina et al. (10) reported their retrospective experience with 11C-Choline PET in a cohort of intermediate, high and VHR patients. They report low sensitivities for the detection of nodal disease both on medium and high-risk patients, with 17% and 40% in a region-based analysis, respectively. However, in a subgroup of 28 VHR patients where 50% harbored nodal disease, the test performance was better, with sensitivity, specificity, positive predictive value and negative predictive value of 71%, 93%, 91% and 76%, respectively.
In our sub-analysis of 9 patients with ≥ 3 positive lymph nodes on high-quality ePLND, ^{18}F-fluorocholine PET/CT on a patient-based analysis had sensitivity, specificity, PPV and NPV of 66.7%, 77.1, 42.9, and 90.0%, respectively. This was similar to our results in the overall VHR PCa population, with a high NPV pointing to a potential role as means of excluding ≥ 3 positive lymph nodes disease. As the number of patients in this group was low (n=9) it would be interesting to see multicenter results in this subgroup, as the presence of ≥ 3 positive lymph nodes has been suggested as an independent risk factor for both biochemical recurrence and metastatic progression, with these patients benefiting from adjuvant treatment after surgery (15).
More recently, some studies have shown promise of good results with PSMA PET/CT staging in the treatment-naïve high-risk patients. *Hope et al.* (16) performed a trial which enrolled 764 patients with intermediate and high-risk PCa being considered for prostatectomy at a single institution, who performed ^{68}Ga-PSMA-11 PET/CT prior to intervention. 277 patients ended up receiving radical prostatectomy with extended lymph node dissection, in which the PET sensitivity, specificity, positive predictive value and negative predictive value were of 40% (95% CI, 34-46%), 95% (95% CI, 92-97%), 75% (95% CI, 70-80%) and 81% (95% CI, 76-85%), respectively.
Hofman et al. (17) published the results of probably the most important study so far, the proPSMA trial. This was a multicenter randomized controlled trial in 10 Australian hospitals. 302 patients with high-risk PCa were randomly selected for either usual imaging or ^{68}Ga-PSMA-11 PET/CT. PSMA PET performed better than CT scan, and very well, with an 85% (95% CI, 74-96%) sensitivity and 91% (95% CI, 85-97%) specificity for nodal disease. Also, although patients who underwent PSMA PET as staging method didn't undergo classical staging previously, the exam results are reported to have changed the clinical preferred options in 28% of patients, with 14% being directed from curative to palliative treatment, 7% with a change in radiotherapy technique and 7% with a change in surgical technique.
Our work analyzed a real-life experience of a region and country where availability of ^{68}Ga-PSMA-11 PET/CT is scarce and ^{18}F-fluorocholine is widespread. As such, many of our patients don't have the option for the newest but less accessible radiotracer. For that reason, it was important for us to understand the value caretakers are providing VHR PCa patients regarding staging imaging.
It comes with the limitations of being a retrospective study, which includes patients operated in a single center, with imaging being performed in many centers. The inclusion of only patients who underwent RALP + ePLND may have selected patients with less advanced localized disease stages, more amenable for radical prostatectomy as a treatment choice; and also excluded metastatic patients and radiotherapy patients who didn't have surgery.
The analysis of ^{18}F-fluorocholine PET/CT accuracy was also only made by patient and side, and using every lymph node region separately, as our current technique of ePLND retrieves all nodes of a side all together in a single packet.
Reviewing our data is important to understand what real life results we get when using ^{18}F-fluorocholine PET/CT in VHR patients, and we found that even though the exam specificity and NPV were > 80%, its low sensitivity both on patient (64.3%) and side (35.0%) based analysis are not enough to consider the exam as a "*game changer*", even in the VHR PCa group.
After the first data on new imaging modalities emerged, some studies started suggesting the wide-spread study of new tracers, such as ^{177}Lu-PSMA (18) and government approval of PET/CT for staging (19), which should facilitate the increasing the availability and decreasing the costs of those exams.
As such, efforts to advance the knowledge in the field and maintain low-cost accessibility to exams considered clinically useful should be pursued continuously.

Conclusions

We conclude that ^{18}F-fluorocholine PET/CT as staging for patients with VHR localized PCa doesn't meet the criteria to be a standard exam for pre-operative staging. We therefore believe new radiotracers such as the ^{68}Ga-PSMA-11 should continue to be assessed in this setting. Governments and health services should also make efforts to ensure that new meth-ods of imaging with clinical utility have a reasonable financial cost and availability.

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