Original Study

The Prognostic Role of Preoperative PSMA PET/CT in cN0M0 pN+ Prostate Cancer: A Multicenter Study

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Abstract

PET/CT have improved the detection of lymph node involvement in patients with prostate cancer at staging. We aimed to investigate the prognostic value of preoperative PET/CT in patients with node negative at conventional imaging and node positive at radical prostatectomy (RP). We included 1163 patients with these features from 17 referral centers. 95 and 100 patients had preoperative PSMA and/or Choline PET/CT, respectively. Node positive patients at PSMA PET/CT with negative conventional imaging have an increased risk of systemic progression after RP compared to node negative patients both at conventional and/or molecular imaging. No significant results were highlighted for Choline PET/CT.

Context: Despite negative preoperative conventional imaging, up to 10% of patients with prostate cancer (PCa) harbor lymph-node involvement (LNI) at radical prostatectomy (RP). The advent of more accurate imaging modalities such as PET/CT improved the detection of LNI. However, their clinical impact and prognostic value are still unclear. We aimed to investigate the prognostic value of preoperative PET/CT in patients node positive (pN+) at RP. **Evidence Synthesis:** We retrospectively identified cN0M0 patients at conventional imaging (CT and/or MRI, and bone scan) who had pN+ PCa at RP at 17 referral centers. Patients with cN+ at PSMA/Choline PET/CT but cN0M0 at conventional imaging were also included. Systemic progression/recurrence was the primary outcome; Cox proportional hazards models were used for multivariate analysis. **Evidence Acquisition:** We included 1163 pN+ men out of whom 95 and 100 had preoperative PSMA and/or Choline PET/CT, respectively. ISUP grade ≥4 was detected in 66.6%. Overall, 42% of patients had postoperative PSA persistence (≥0.1 ng/mL). Postoperative management included initial observation (34%), ADT (22.7%) and adjuvant RT+/-ADT (42.8%). Median follow-up was 42 months. Patients with cN+ on PSMA PET/CT had an increased risk of systemic progression (52.9% vs. 13.6% cN0 PSMA PET/CT vs. 21.5% cN0 at conventional imaging; $P < .01$). This held true at multivariable analysis: (HR 6.184, 95% CI: 3.386-11-295; $P < .001$) whilst no significant results were highlighted for Choline PET/CT. No significant associations for both PET types were found for local progression, BCR, and overall mortality (all $P > .05$). Observation as an initial management strategy instead of adjuvant treatments was related with an increased risk of metastases (HR 1.808; 95% CI: 1.069-3.058; $P < .05$). **Conclusions:** PSMA PET/CT cN+ patients with negative conventional imaging have an increased risk of systemic progression after RP compared to their counterparts with cN0M0 disease both at conventional and/or molecular imaging.

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Introduction

Despite a preoperative negative conventional imaging (cN0M0), more than 10% of patients with prostate cancer (PCa) are diagnosed with lymph node involvement (pN+) at radical prostatectomy (RP).[1–3] The sole randomized controlled trial (RCT) analyzing optimal post-RP management in pN+ patients was performed in the pre-PSA era[4,5] and included men with relatively high pathological burden. Therefore, the management of pN+ patients is still based on low quality evidence, with most recent data suggesting a risk-based strategy, ranging from expectant management with eventual early salvage treatments in case of relapse, for those with less aggressive disease, to adjuvant local and/or systemic treatments for those at a higher risk.[6,7]

Lymph-node involvement generally yields aggressive PCa features.[7] Recently, conventional staging including axial imaging (CT scan and/or mpMRI) and bone scan is being challenged by the advent of new nuclear medicine imaging-based techniques, namely PSMA PET/CT and Choline PET/CT. Improved accuracy of PSMA compared to conventional imaging for the detection of PCa lymph node metastasis has been proven in the primary staging, as well as in the recurrent setting.[8–12] Hence, with the increasing evidence and use of these imaging modalities, conventional imaging is likely to be replaced in the next decade.[8,12] Multiple studies have shown that PSMA PET/CT has a moderate sensitivity but very high specificity for detection of nodal metastasis in intermediate-to-high-risk PCa.[9–11] Choline PET/CT is less accurate compared to PSMA-PET.[13] Nonetheless, it has increased accuracy compared to conventional imaging.[14] Both CT and MRI have an equally poor performance in detecting lymph node involvement.[15] With the increase in use of PET/CT, more pN+ men will be diagnosed with positive nodes preoperatively, with a stage migration towards cN+ PCa. However, whether lymph node positivity at new imaging modalities has a negative prognostic role or not remains unknown. Similarly, whether a patient with preoperative negative staging at PET/CT subsequently found with pN+ may have an improved course compared to those negative at conventional imaging only has not been demonstrated. Hence, we performed a multicenter retrospective study with the aim of assessing the prognostic role of PSMA and Choline PET/CT in the context of men being diagnosed with pN+ PCa together with a preoperative negative conventional imaging (cN0M0). This could guide future adjuvant or salvage decision-making.

Methods

Study Population

We retrospectively collected the data of men with PCa being found pN+ after primary radical prostatectomy (RP) with lymphadenectomy and preoperative negative staging at conven-

tional imaging (mpMRI and/or CT and bone scan – cN0M0) from 17 tertiary referral centers between 2001 and 2021. Patients with cN+ at preoperative PSMA and/or Choline PET/CT but negative conventional imaging were also included. Additional exclusion criteria were: hormonal therapy or radiation therapy (RT) performed before surgery, RP performed before the year 2000, and patients with important baseline features missing, including postoperative follow-up information, preoperative PSA and preoperative staging.

Covariates and Outcomes

PSA persistence was defined as PSA ≥0.1 ng/mL at 6 weeks post-op; Biochemical recurrence (BCR) as PSA ≥0.2 ng/ml and 2 consecutive raises or PSA persistence; Systemic progression/recurrence as a lymph-node/bone/visceral progression of disease at follow-up imaging; Local progression as progression to prostatic bed (imaging or palpable disease); castration resistance as 3 consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA>2 ng/mL despite castrate serum testosterone.

The primary outcome was to assess whether PSMA PET/CT and/or Choline PET/CT positive and/or negative patients have higher or lower rates of systemic progression respectively, compared to men who received conventional staging only. Secondary outcomes were overall survival, local-progression, and BCR-free survival. Cancer-specific survival and PSA persistence were also assessed. Real-life patterns of management of patients who were diagnosed with pN+ disease at RP were also reported.

Statistical Analysis

Analyses were performed with the use of SAS 9.4 TS Level 1M7 statistical analysis software for Windows. Continuous variables are expressed as median with interquartile range, and categorical variables are reported as count and percentages. In univariate analysis comparisons between groups were performed using Wilcoxon-Mann–Whitney or Kruskal-Wallis tests. Comparisons of percentages were performed using Chi-square or Fisher's exact tests depending on the distribution of the data. Kaplan-Meier method was used to estimates curves for systemic progression/recurrence-free, local progression/recurrence-free and overall mortality-free rate; survival curves were compared using the Log-rank test. To assess which variables were risk factors for oncological outcomes different multivariable Cox models were performed. For each model results were expressed with the estimate of the Hazard Ratio (HR) and the relative confidence interval at a level of 95% (CI 95%). Curves were compared with the Log Rank test.

Results

Baseline Features

Overall, we included 1163 patients (Table 1 and Supplemental Table 1 for detailed analysis and Choline PET subgroups). The median age at RP was 65 years/old (IQR 61-70). At RP more than half of men had seminal vescicle invasion (59.8%) or ISUP ≥4 (66.6%) or positive margins (55.0%). Considering patients who underwent PSMA-PET, Choline-PET and conventional imaging only, no major differences were present with exceptions for pre-RP PSA (higher for Choline positive men, $P < .01$), a more recent surgery date and higher rate of robotic procedures for those having a preoperative PSMA ($P < .01$). A significantly different number of removed nodes was present between subgroups; the highest median number of collected lymph nodes was observed in patients with positive novel imaging ($P < .05$). Furthermore, cN+ men at PSMA or Choline had a higher number of positive nodes compared to the other subgroups (both $P < .01$). The median number of positive nodes was higher for patients cN+ at PSMA or Choline PET/CT versus a those cN0 at PSMA or Choline-PET and at conventional imaging alone ($P < .05$). Interestingly, those with a positive preoperative PET PSMA (40.6%) or Choline (32.1%) had a higher rate of internal iliac nodes being positive compared to the other subgroups (both $P < .05$).

Oncological Results

Oncological results are shown in Table 2 (and Supplemental Table 2 for detailed analysis and Choline PET subgroups). Median follow up was 42 months (IQR 23-69). Overall, 34.4% underwent initial observation. Proportions differed from 66.7% for patients cN0 at PSMA PET/CT to 30.3% for PSMA-PET cN+ PCa ($P < .001$); this was not true for Choline-PET ($P = .17$). PSA-persistence rate was higher in cN+ PSMA PET/CT (52.9% vs cN0 PSMA PET 28.1% vs cN0 conventional imaging alone 42.6%; $P = .042$). Similarly, a higher number of men had local ($P = .025$) and systemic ($P < .001$) progression in the cN+ PSMA PET/CT group (local 14.7%; systemic 52.9%) compared to negative preoperative staging at PSMA PET/CT (local 0%; systemic 13.6%) and conventional imaging alone (local 7.7%; systemic 21.5%). Time to systemic progression was also significantly shorter for PSMA-PET/CT positive patients ($P < .001$). No major differences were noted amongst Choline-PET subgroups except for a longer time to death in men with a negative preoperative Choline-PET ($P = .049$). At last follow up 2.4% of men died due to PCa and 2.4% for PCa unrelated causes. No correlations with mortality were highlighted (all $P > .05$).

Uni- and Multivariable Analysis

Survival Kaplan-Meier curves stratified for PSMA PET/CT results for systemic progression/recurrence, local progression/recurrence and overall mortality are shown in Figure 1. Univariable analyses are available as Supplemental Table 3. On multivariate analysis (Table 3), patients with positive nodes at preoperative PSMA PET/CT (cN+), compared to those who did not undergo PSMA-PET imaging, had a higher likelihood of systemic progression/recurrence (HR 6.184, 95% CI: 3.386-11.295; $P < .001$). Higher chances of systemic progression were observed also in case of PSA persistence (HR 2.336, 95% CI: 1.510-3.612; $P < .001$) and in case of observation as initial management strategy (HR 1.808, 95% CI: 1.069-3.058; $P = .0273$). Patients who underwent observation as an initial management strategy had a higher likelihood of undergoing local recurrence: HR 3.818 ($P = .0779$) if compared with ADT+RT. No statistically significant associations were observed for overall mortality ($P > .05$).

PSMA-PET Imaging

No major baseline differences were noted amongst those who had or not a preoperative PSMA-PET imaging (Supplemental Table

Table 1 Descriptive Statistics and Population Characteristics for PSMA PET/CT and Choline PET/CT Baseline Features of the Cohort of 1163 Patients With Lymph Node–Positive Prostate Cancer

Variable	ALL	PSMA-PET -% (n) / Median (IQR) CI 95% CI: 95%			
		Positive (cN+)	Negative (cN0)	Others	*P*
N		35	60	1068	
Age at RP *(ys)*	65 (61-70)	67 (62-70) (65;68)	66 (62-72) (65;68)	65 (60-70) (64;65)	.1035
Pre-RP PSA *(ng/mL)*	11.1 (7.1-20.0)	10.8 (7.1-28.6) (12;36)	11.3 (8.0-20.0) (13;28)	11.1 (7.1-20) (16;18)	.7989
Pre-RP imaging results					
Negative	46.2 (534)	0.0 (0)	0.0 (0)	50.3 (534) (47;53)	**≤.01**
Positive prostate only	48.3 (558)	0.0 (0)	98.3 (59) (95;100)	47 (499) (44;50)	
Positive nodes only (cN+ PET)	0.5 (6)	2.9 (1) (0;8)	1.7 (1) (0;5)	0.4 (4) (0.01;0.8)	
Positive prostate + nodes (cN+ PET)	5.0 (58)	97.1 (34) (92;100)	0.0 (0)	2.3 (24) (1;3)	
Radical prostatectomy - prostate features					
Date					
<2010	4.9 (57)	0.0 (0)	0.0 (0)	5.3 (57) (4;7)	**≤.01**
2010-2015	42.3 (492)	0.0 (0)	0.0 (0)	46 (492) (43;49)	
2016-2021	52.8 (614)	100.0 (35)	100.0 (60)	48.6 (519) (46;52)	
ISUP					
1	2.2 (26)	0.0 (0)	0.0 (0)	2.4 (26) (2;3)	.4784
2	7.8 (91)	8.6 (3) (0;18)	5.1 (3) (0;11)	7.9 (85) (6;10)	
3	23.3 (271)	17.1 (6) (5;30)	30.5 (18) (19;42)	23.2 (247) (21;26)	
4	27.8 (323)	37.1 (13) (21;53)	20.3 (12) (10;31)	27.9 (298) (25;31)	
5	38.8 (450)	37.1 (13) (21;53)	44.1 (26) (31;57)	38.5 (411) (36;41)	
pT stage					
pT2	10.6 (123)	2.9 (1) (0;8)	8.5 (5) (1;16)	10.9 (117) (9;13)	.4772
pT3a	29.6 (344)	25.7 (9) (11;40)	28.8 (17) (17;40)	29.8 (318) (27;33)	
pT3b	59.8 (694)	71.4 (25) (57;86)	62.7 (37) (50;75)	59.2 (632) (56;62)	
Surgical margins					
Negative	45.0 (520)	51.5 (17) (34;69)	39.0 (23) (27;51)	45.0 (480) (42;48)	.4870
Positive	55.0 (635)	48.5 (16) (31;66)	61.0 (36) (49;73)	55.0 (583) (52;58)	
Radical prostatectomy - lymph nodes features					
LAD					
Limited	10.4 (121)	0.0 (0)	0.0 (0)	11.4 (121) (9;13)	≤.01
Extended limited	35.6 (412)	60.0 (21) (44;76)	35.0 (21) (23;47)	34.8 (370) (32;38)	
Extended	51.6 (598)	34.3 (12) (19;50)	61.7 (37) (49;74)	51.7 (549) (49;55)	
Retroperitoneum	2.3 (27)	5.7 (2) (0;13)	3.3 (2) (0;8)	2.1 (23) (1;3)	
Nodes removed	19 (13-27)	25 (17-34) (21;31)	21 (15-31) (20;26)	19 (13-27) (20;21)	**.0108**
Nodes positive	1 (1-3)	2 (1-4) (2;5)	1 (1-2) (1;2)	1 (1-3) (2;3)	**.0073**
Nodes positive laterality					
Unilateral	65.8 (684)	57.1 (20) (41;74)	77.2 (44) (66;88)	65.4 (620) (62;68)	.1044
Bilateral	34.2 (356)	42.9 (15) (26;59)	22.8 (13) (12;34)	34.6 (328) (32;38)	

^The patient was cN+ at Choline PET/CT.
Abbreviations: cN+ = clinically positive lymph-nodes at PET preoperative staging; PSA = prostate-specific antigen; RP = radical prostatectomy; pT stage = pathological T stage; LAD = lymphadenectomy; limited = obturator only; extended limited = external iliac+obturator; extended = at least external, internal, obturator and presacral.
Positive prostate: any imaging - mpMRI and/or CT scan and/or PET/CT.

4) with the exception of an earlier year of surgery and lower rates of minimally invasive procedures, extended lymphadenectomy and number of nodes removed (all $P < .05$) for those not having preoperative PSMA-PET. Men receiving preoperative PSMA-PET also had a shorter follow up, an increased rate of postoperative observation as initial management strategy and of radiation therapy as adjuvant/early salvage strategy (all $P < .05$ - Supplemental Table 5).

Discussion

In this retrospective observational multicentric study we analyzed treatment patterns and prognostic value of novel imaging in a large

Table 2 Descriptive Statistics and Population Characteristics for PSMA PET/CT and Choline PET/CT Results for Follow-Up and Oncological Results of the Cohort of 1163 Patients With Lymph Node Positive Prostate Cancer

Variable	ALL	PSMA-PET -% (n) / Median (IQR) CI 95% CI: 95%			
		Positive (cN+)	Negative (cN0)	No PSMA	*P*
n		35	60	1068	
Postoperative results					
PSA persistence	42.1 (478)	52.9 (18) (36;70)	28.1 (16) (16;40)	42.6 (444) (40;46)	**.0400**
Management					
Initial management strategy					
Observation	34.4 (392)	30.3 (10) (15;46)	66.7 (38) (54;79)	32.8 (344) (30;36)	**≤.01**
Adjuvant ADT	22.7 (259)	21.2 (7) (7;35)	3.5 (2) (0;8)	23.8 (250) (21;26)	
Adjuvant RT alone	10.8 (123)	18.1 (6) (5;31)	10.5 (6) (3;19)	10.6 (111) (9;12)	
Adjuvant RT+ADT	32.0 (365)	30.3 (10) (15;46)	19.3 (11) (9;30)	32.8 (344) (30;36)	
Outcomes					
If BCR PSA doubling time	4.4 (2.8-7.2)	4.3 (3-6) (2;6)	5.2 (2.5-8.5) (4;9)	4.5 (3-8) (5;11)	.8569
Salvage treatment if BCR					
No, observation	11.3 (27)	14.3 (1) (0;40)	14.3 (3) (0;29)	10.9 (23) (7;15)	**≤.01**
RT alone	18.1 (43)	28.6 (2) (0;62)	52.3 (11) (31;74)	14.3 (30) (10;19)	
RT+ADT	36.1 (86)	28.6 (2) (0;62)	23.8 (5) (6;42)	37.6 (79) (31;44)	
Lifelong ADT	34.5 (82)	28.6 (2) (0;62)	9.5 (2) (0;22)	37.1 (78) (30;43)	
Local progression/recurrence	7.6 (84)	14.7 (5) (3;27)	0.0 (0)	7.7 (79) (6;9)	**.0252**
time (mo)	28 (6-55)	4 (3-9)	-	34 (7-56)	0.0690
Systemic progression/recurrence	22.0 (246)	52.9 (18) (36;70)	13.6 (8) (5;22)	21.5 (220) (19;24)	**≤.01**
time (mo)	28 (11-58)	5.5 (1-28)	18 (3-52)	35 (1-162)	**≤.01**
Status at follow up					
Alive, no evidence of disease without ADT	33.5 (382)	38.2 (13) (22;55)	40.7 (24) (28;53)	32.9 (345) (30;36)	.7686
Alive, hormone sensitive disease ± ADT	55.9 (638)	58.8 (20) (42;75)	52.5 (31) (40;65)	56.1 (587) (53;59)	
Alive, CRPC with no sec line therapies	1.1 (13)	0.0 (0)	0.0 (0)	1.2 (13) (0.6;2)	
Alive, CRPC under sec line therapies	4.4 (51)	0.0 (0)	1.7 (1) (0;5)	4.7 (50) (3;6)	
Death, Pca specific	2.4 (28)	2.9 (1) (0;9)	1.7 (1) (0;5)	2.5 (26) (2;3)	
Death, NON Pca specific	2.4 (28)	0.0 (0)	3.4 (2) (0;8)	2.5 (26) (2;3)	
Last fu time(mo) from RP	42 (23-69)	23 (16-36) (21;31)	26 (10-37) (21;30)	46 (24-72) (49;53)	**≤.01**
Death					
Pca specific	2.4 (28)	2.9 (1) (0;9)	1.7 (1) (0;5)	2.5 (26) (2;3)	.8720
NON Pca specific	2.4 (28)	0.0 (0)	3.4 (2) (0;8)	2.5 (26) (2;3)	
Time to death *(mo)*	43 (24-69)	24 (17-36) (22;31)	27 (11-39) (22;31)	48 (24-72) (50;54)	**≤.01**

Abbreviations: ADT = androgen deprivation therapy; BCR = biochemical recurrence (defined as PSA ≥ 0.2 and 2 consecutive raises); CRPC = castration resistant prostate cancer; FU = follow up; mo = months; PSA = prostate specific antigen; PSA = persistence: first postoperative PSA ≥0,1ng/mL at least 1 month after RP; RT = radiation therapy.
cN+ = clinically positive lymph-nodes at PET preoperative staging; cN0 = clinically negative lymph-nodes at PET preoperative staging.

cohort of patients diagnosed with pN+ PCa at RP. Our findings suggest that PCa patients with lymph node invasion with a positive PSMA PET/CT are at higher risk of experiencing recurrence as compared to their counterparts with a negative PET or those who were not staged with this imaging modality.

There are several key findings. First, when PSMA-PET performed on patients with cN0M0 on conventional imaging showed cN+ disease, it was a hallmark of more aggressive disease and from this point those patients must be consequently considered as having a worse prognosis. This may also suggest patients harboring node metastasis detected by PSMA-PET (5 mm or larger, with high PSMA expression)[16] and invisible on conventional imaging may represent a novel prognostic category which claims further investigation to define its optimal management. While current evidence suggests that patients with clinical pelvic lymph node involvement on conventional imaging have worse prognosis compared to those not clinically-metastatic, up to now there is no evidence on patients diagnosed using novel imaging.[17]

Second, we did not find any prognostic value of negative PSMA-PET. PSMA should miss less significant disease compared to conventional imaging due to its improved diagnostic accuracy[8]; hence, someone might expect improved results for someone with negative PSMA compared to negative conventional imaging only.

Table 3 Multivariable Cox Regression Analysis Predicting Systemic Progression/Recurrence, Local Progression/Recurrence and Overall Mortality for 1163 pN1 Prostate Cancer Patients Treated With Radical Prostatectomy and Lymph Node Dissection

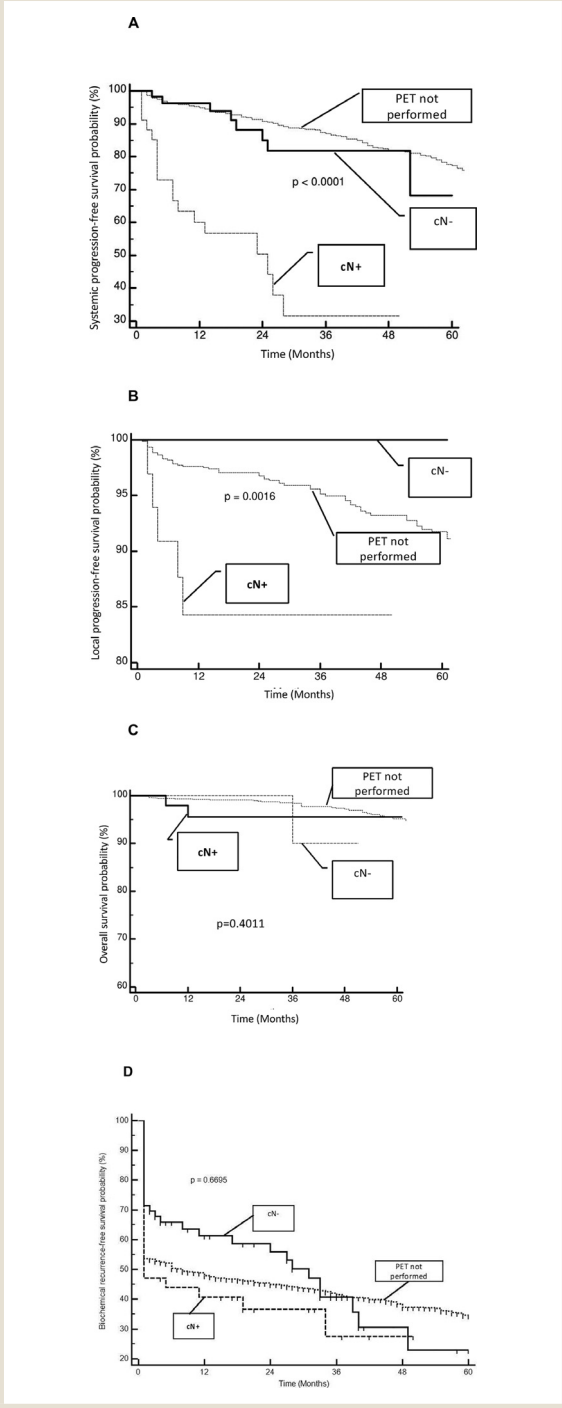
	Systemic Progression/Recurrence		Local Progression/Recurrence	
	Multivariate - n = 1038		Multivariate - n = 1032	
Variable	Hazard Ratio (CI)	*P*	Hazard Ratio (CI)	*P*
PSMA-PET				
Postive (cN+)	6.184 (3.386-11.295)	≤.0001	2.649 (0.0929-7.554)	.0684
Negative (CN0)	0.890 (0.298-2.660)	.8354	-	
No PSMA	1.0		1.0	
Age				
ASA Score				
Rp Date				
<2010	0.311 (0.099-0.975)	.0451		
2010-2015	0.426 (0.277-0.656)	.0001		
2016-2021	1.0			
Approach				
Open retropubic			0.571 (0.151-2.161)	.4096
Laparoscopic			0.725 (0.149-3.519)	.6902
Robotic			1.0	
Path ISUP				
1	1.0		1.0	
2	0.822 (0.228-2.971)	.7654	0.994 (0.122-8.130)	.9959
3	1.049 (0.289-3.808)	.9415	0.472 (0.055-4.032)	.4930
4	1.786 (0.470-6.786)	.3944	0.856 (0.092-7.942)	.8908
5	2.422 (0.597-9.822)	.2157	1.921 (0.185-19.932)	.5845
pT stage^				
2				
3a				
3b				
Surgical margins				
Negative				
Positive				
Number of positive nodes	0.998 (0.943-1.055)	.9353	1.012 (0.900-1.138)	.8435
PSA persistence				
No	1.0		1.0	
Yes	2.336 (1.510-3.612)	.0001	1.768 (0.630-4.956)	.2788
Initial management				
Observation	1.808 (1.069-3.058)	.0273	3.818 (0.861-16.932)	.0779
ADT	1.020 (0.651-1.600)	.9301	1.851 (0.603-5.680)	.2817
RT	0.886 (0.519-1.513)	.6569	0.968 (0.246-3.786)	.9584
ADT+RT	1.0		1.0	

Abbreviations: ^pT stage = pathological T stage (considered as a continue variable in the multivariable analysis); RP = radical prostatectomy; PSA persistence: first postoperative PSA ≥0,1ng/mL at least 1 month after RP; ADT = androgen deprivation therapy; RT = radiation therapy; - = no events for the variable.

However, according to our findings, an absence of nodal uptake in men subsequently found with pathologically positive node should not be considered differently compared to those with preoperative conventional imaging.

Third, we are also the first to report on a consistent number of men with PSMA-negative results and subsequently found with positive nodes. Interestingly, baseline PCa features did not show major differences compared to those with only conventional imaging being negative or with those having node-positive preoperative PSMA, with the exception of the number of positive nodes. Although we cannot derive the incidence of pN+ based on our series, as we selected patients based on nodal status, LAD should not be abandoned upfront in all men with a negative preoperative PSMA and high risk of nodal invasion. Our findings are in line with

Figure 1 Kaplan-Meier curves depicting: systemic progression/recurrence-free rate (1A); (1B) local progression/recurrence-free rate in 1163 patients with pN1 prostate cancer; (1C) Overall mortality-free rate in 1163 patients with pN1 prostate cancer. cN+ = clinically positive lymph-nodes at PSMA PET/CT preoperative staging; cN0 = clinically negative lymph-nodes at PET preoperative staging; PET not performed = conventional imaging only



a recent trial reporting low sensitivity of PSMA-PET/CT for the detection of nodal metastasis.[18]

Fourth, our study also provides real world evidence showing new imaging modalities strongly impact the extent of lymphadenectomy and post-RP management. Men with positive PSMA-PET and Choline-PET had on median 6-7 more nodes removed than patients who underwent CT/BS only. Furthermore, two-thirds of patients with negative PSMA-PET initially underwent surveillance; the same approach was chosen only in one-third of patients with positive PSMA-PET, who were mostly managed post-op by RT and/or ADT. Interestingly, observation was also related to an increased risk of recurrence. This highlights the need of new tools to better identify those suitable for initial expectant management, without decreasing oncological outcomes. Although further studies are needed, pre- and postoperative PSMA may potentially refine patient selection in this context.

From a clinical perspective, we lack evidence on optimal management in a case of PSMA-related clinical upstaging and there is uncertainty if PSMA-PET may improve oncologic outcomes.[19] In our study, we found that PSMA-PET performed prior to radical prostatectomy has strong implications. Patients with preoperatively positive nodes, subsequently confirmed by pathological analysis, should be informed on a higher risk of progression despite surgery, and, possibly, the need to undergo early adjuvant radiation therapy and intensified follow-up. On the contrary, a negative preoperative PSMA-PET does not always rule out pN+ disease, and men subsequently diagnosed with pN+ disease seem to have a similar prognosis of those with negative conventional imaging. Until development of new PSMA-PET based validated nomogram patients with negative PSMA-PET should still undergo pelvic lymph node dissection, when indicated by well-established clinicopathologic factors.[20]

From a research perspective, we highlighted novel imaging performed for primary staging influences decision-making post-RP within a pN+ context despite long-term impact of PSMA-PET remains to be understood and optimal pN+ management remains unclear. These results are in line with a recent survey, showing PSMA-PET is already strongly implemented in clinical decision making, when available (Marra et al, Clin Gen Cancer, in press). In a previous systematic review, Marra et al. underlined that pN+ PCa is an extremely heterogeneous and multifaceted group where one approach does not fit all.[6] Several studies found that Gleason score, PSA value, pT stage, positive surgical margins, number of involved lymph nodes, and their size impact oncologic outcomes.[6] Considering patient-adapted strategy, we believe PSMA-PET may be an additional tool, along with clinicopathological features to distinguish between aggressive versus more favorable PCa amongst those with positive nodes at final pathology. Therefore, research should promptly evaluate the impact of novel imaging and focus on possible gaps, such as biomarkers and advanced risk stratification tools for imaging-undetectable metastatic disease. Importantly, our work did not include men with cN+ PET imaging subsequently being found with negative nodes at final pathology which also represents another aspect of novel imaging that requires further investigation.

Some limitations have to be acknowledged. This is a retrospective, multi-center study, which may be associated with selection bias.

Furthermore, we lacked a central imaging and pathology review, which, however it was performed by high-volume dedicated radiologists, nuclear medicine physicians and pathologists at each tertiary center. Overall the follow-up was relatively short, with longer follow up needed to show meaningful differences in major oncological outcomes. The number of men with preoperative PET imaging was also small to draw meaningful conclusion and our results are mainly to be considered as hypothesis generating for future studies. Also, despite performing multivariate analysis, the same management options in pN+ patients undergoing preoperative PSMA may have differed in those not undergoing it as they were applied in different historical periods, possibly introducing further bias. Nevertheless, we present the first study which provides encouraging evidence on the association between cN+ disease on PSMA-PET and systemic progression after radical prostatectomy, as well as the impact of PSMA-PET on post-op treatment decision making.

Conclusions

Amongst men being found with pN+ nodes after RP and LAD, those with a preoperative PSMA PET/CT scan showing positive nodes despite a negative conventional imaging may have an increased risk of systemic progression whilst those with negative PSMA have similar prognosis to those with negative conventional imaging.

Clinical Practice Points

- The optimal management of cN0M0 at conventional imaging prostate cancer patients, subsequentially found with lymph node involvement (pN+) at radical prostatectomy remains unclear and a gold standard treatment does not exist.
- New imaging modalities including PSMA-PET/CT are increasingly used in a preoperative staging phase.
- The current work aimed to investigate the prognostic value of preoperative PET/CT in patients' node positive (pN+) at RP in order to guide subsequent therapeutic management.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2023.11.006.

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