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^{11}C-choline PET/CT in recurrent prostate cancer: retrospective analysis in a large US patient series

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ABSTRACT

Purpose: To evaluate ^{11}C-choline PET/CT detection performance for biochemically recurrent prostate cancer (PCa) in a large non-European cohort in the context of emerging evidence for PSMA PET in this setting, and to map patterns of PCa recurrence.

Methods: We retrospectively analyzed ^{11}C-choline PET/CT scans from 287 patients who were enrolled onto an imaging protocol based on rising prostate-specific antigen (PSA) levels (mean:3.43 ng/mL, median:0.94 ng/mL, range:0.15–89.91) and suspected recurrent PCa. A total of 187 patients had undergone primary radical prostatectomy (RP; 79/187 had secondary radiotherapy), 30 had undergone primary radiotherapy (RT), and 70 had persistent PSA elevation after receiving initial treatment (69 post-RP, 1 post-RT). The level of suspicion for recurrence on ^{11}C-choline PET/CT was scored (0:negative, 1:equivocal, 2:positive) by two readers. The correlation between ^{11}C-choline PET/CT positivity and initial treatment, Gleason score, NCCN stage, PSA level, PSA doubling time, PSA velocity, and time between initial treatment and PET imaging was evaluated. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria were used to map ^{11}C-choline recurrence patterns.

Results: Considering scores 1 and 2 as positives, consensus between the two readers deemed 66% of the ^{11}C-choline PET/CT scans as positive. When sorted by PSA level, 45% of patients with PSA<0.5 ng/mL, 56% of patients with PSA 0.5–0.99 ng/mL, 70% of patients with PSA 1.0–1.99 ng/mL, and 90% of patients with PSA ≥2.0 ng/mL scored either 1 or 2 on ^{11}C-choline PET/CT scans. When considering scores of 2 only, ^{11}C-choline PET/CT positivity was 54% (28%, 46%, 62%, and 81%, respectively, for patients with PSA <0.5 ng/mL, 0.5–0.99 ng/mL, 1.0–1.99 ng/mL, and ≥2.0 ng/mL). In multivariate analysis, only the PSA level was significantly associated with scan positivity. Pattern analysis showed that pelvic lymph nodes were the most common site of

recurrence, and 28% of patients had ^{11}C-choline-positive suspected recurrences outside the initial treatment field.

Conclusion: ^{11}C-choline PET/CT can detect PCa recurrence even among patients with low PSA levels when interpretation accounts for the clinical context, providing a certain pre-test probability. Until PSMA agents are fully approved for PCa, choline PET/CT may provide clinical utility.

KEYWORDS: ^{11}C-choline PET/CT, recurrence, prostate cancer, prostate-specific antigen, PSA relapse

INTRODUCTION

Recurrent prostate cancer (PCa) following primary therapy is common (*1, 2*). The choice of local versus systemic treatment in this setting depends on the location of the recurrence (*3-5*). Hence, early detection of recurrence and differentiation between local versus systemic recurrence are important.

Current conventional imaging studies are suboptimal to detect recurrent PCa, especially when PSAs levels are low (*2-4, 6, 7*). In recent years, PET/CT with ^{11}C-choline or ^{18}F-choline have changed the management of recurrent PCa and have been commonly used for early recurrence detection, particularly in Europe (*8, 9*). However, choline PET has a low detection rate for PSA levels<1.0 ng/mL (*10-12*). More recently, PET/CT with ^{68}Ga or ^{18}F-PSMA agents is gaining traction for early PCa recurrence detection (*13-17*) and has replaced choline PET/CT at some institutions. Although PSMA PET is now routinely used in several countries, it is not currently approved for commercial use in the US and many other countries. In contrast, ^{11}C-choline was approved by the US FDA in 2012 under an IND (*18*). Until PSMA agents are fully approved for PCa, choline PET/CT may provide clinical utility in PCa. We therefore conducted a large retrospective analysis of ^{11}C-choline PET/CT data for patients with recurrent PCa.

MATERIALS AND METHODS

Patients

Patients with biochemical recurrence after biopsy-proven PCa initially treated with curative intent were enrolled in an IRB-approved ^{11}C-choline PET/CT expanded access study (protocol #15-117), with a primary objective to localize sites of recurrence. From our data base, we retrieved patients scanned between March 2016 (opening of protocol) and December 2017 and retrospectively

analyzed patients who were treated initially by radical prostatectomy (RP), radiation therapy (RT), or RP+RT, with biochemical recurrence or persistently elevated PSA and prior negative or equivocal other imaging studies (prior tests were performed at the discretion of the treating physicians). Biochemical recurrence was defined as PSA>0.2 ng/ml over two sequential tests, two weeks apart (for patients post-RP) and PSA≥2.0 ng/mL above the post-therapy nadir (for patients post-RT). Patients initially treated by other local therapies or treated for metastatic disease were excluded. All patients provided written informed consent.

^{11}C-choline PET/CT

^{11}C-choline was synthesized by our Radiochemistry and Molecular Imaging Probe Core Facility. Patients fasted for at least four hours before the scan. A low-dose CT (120 kVp, 80 mAs, and 3.8-mm slice thickness) was acquired from the skull base to the upper thighs. Starting simultaneously with the ^{11}C-choline (370–740MBq) injection, dynamic PET emission images of the lower pelvis were obtained for 5 minutes. This was followed by acquisition of static PET images from the floor of the pelvis to the lower neck, and one final single field-of-view PET image of the lower pelvis. All images were obtained on the Discovery PET/CT systems (GE Healthcare). PET emission data were corrected for attenuation, scatter, and random events, and then iteratively reconstructed into a 128×128×47matrix (voxel dimensions:5.46×5.46×3.27mm^3) using the ordered subset expectation maximization algorithm provided by the manufacturer.

Image analysis

All scans were analyzed using the GE PET VCAR software. Two experienced nuclear medicine physicians interpreted the scans. The first independent reader (LM) (R1) initially interpreted all

scans without access to patients' clinical data (i.e.,'blinded'), and then re-read the scans with access to clinical data (i.e.,'unblinded'). This was followed by a consensus interpretation with the second reader (HS) aware of the patients' clinical history and PSA level. The consensus reading by these two nuclear medicine physicians was used for final analysis.

For each patient, the location and level of suspicion for recurrence were recorded on a 3-point scale: 0–no uptake or uptake considered benign or unrelated to PCa, 1–uptake equivocal (not clearly negative, but not suspicious enough to clearly call recurrence), or 2–uptake consistent with recurrence. PET images were assessed visually. Abnormal uptake was defined as non-physiologic uptake of intensity greater than local background and corresponding to clearly defined anatomic structures on CT. For semiquantitative analysis, maximum standardized uptake value (SUVmax) was recorded, but no specific SUV threshold was applied; rather, visual interpretation was the main criterion to classify findings. Symmetrical inguinal, axillary, and mediastinal lymph nodes (LN) with mild to moderate uptake were considered reactive. A rising PSA level after initial curative therapy implies recurrence, whether detectable or not with current imaging studies. In our primary analysis, we therefore aggregated both scores 1 and 2 as positive. In secondary analysis, we were more stringent and only considered score 2 as positive. To map the patterns of PCa recurrence, we used the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) classification recently proposed for PSMA-ligand PET imaging (*19, 20*).

Statistical analysis

The different readings (blinded and unblinded ratings by R1, as well as the consensus rating) were compared by pairs. The overall reader agreement was measured by both a Cohen's *kappa* coefficient and a weighted *kappa* coefficient using squared weights.

Logistic regression was used to assess the association between the risk of having a positive scan and studied factors (Gleason score 6-7/8/9-10, NCCN grade I-II/III/IV, initial treatment type (RP/RT/persistent elevated PSA after initial treatment), time between scan and initial treatment, PSA level, PSA doubling time, and PSA velocity). A log transformation was used for continuous variables to ensure a less sparse distribution. Variables with p-values<0.20 were introduced in the multivariable model. P-values<0.05 were considered significant. Assessing the patient-based and lesion-based sensitivity, specificity, accuracy, negative predictive value, and positive predictive value analysis was not possible since not all choline- positive lesions were biopsied for histopathological confirmation.

RESULTS

Patient characteristics

Of the 397 consecutive patients who were planned to receive a ^{11}C-choline PET/CT for biochemically recurrent PCa between March 2016 and December 2017 according to the institutional database, 110 patients were excluded (**Fig. 1)**. Therefore, 287 patients were included in this analysis (**Table 1**).

Initial treatments included: (a) RP+/-pelvic lymph node dissection (PLND) (n=108); (b) RP, followed by secondary RT+/-concomitant hormone therapy (HT) (RP+RT) (n=79); and (c) RT+/-concomitant HT (n=30). Another 70 patients had persistently elevated PSA after initial treatment (69 after RP and 1 after RT). None of these 287 patients was undergoing HT at the time of the scan. The mean PSA level at the time of imaging was 3.43 ng/mL (median:0.94 ng/mL, range:0.15–89.9) (**Fig. 2).**

Concordance between readers

The *kappa* coefficient between blinded and unblinded readings by R1 was 0.86, i.e., excellent agreement, while the weighted *kappa* was 0.93. The *kappa* coefficient between unblinded reading by R1 and the consensus reading was 0.76, indicating good agreement, while the weighted *kappa* was 0.87 (**Supplemental Table 1)**. Modifications from score 2 to 0 between unblinded and consensus readings were mainly related to diffuse prostatic uptake after RT. Modifications from score 0 to 1 or 2 between blinded reading and unblinded/consensus readings are shown in **Supplemental Table 2**.

^{11}C-choline PET/CT positivity and proof of recurrence

When scores 1 and 2 were considered positive, the overall detection rate of choline PET/CT was 66% (189/287). When sorted by PSA level, for patients with PSA<0.5 ng/mL, 45%(43/96) were positive. For patients with higher PSA values of 0.5–0.99 ng/mL, 1.0–1.99 ng/mL, and ≥2.0 ng/mL, choline PET/CT positivity was 56%(28/50), 70%(33/47), and 90.5%(85/94), respectively. In univariate analysis, PSA, PSA velocity, and type of treatment were associated with the probability of a positive scan. In multivariate analysis, only PSA level was an independent predictor of scan positivity (p<0.001) (**Supplemental Table 3).** When only score 2 was considered positive, the overall detection rate was 54% (155/287), and 28%, 46%, 62%, and 81% for patients with PSA<0.5 ng/mL, 0.5–0.99 ng/mL, 1.0–1.99 ng/mL, and ≥2.0 ng/mL, respectively. Detection rates are shown in **Figure 3,** case examples in **Figure 4,** and examples of patients in whom choline PET affected management in **Supplemental Table 4**.

Suspected PCa recurrence was confirmed by positive biopsies within 9 months in 49 patients (**Table 2**), by other imaging studies in 72 patients, and by decreasing PSA levels after

therapy in 103 patients (76 salvage pelvic RT+HT, 1 salvage RT, 1 brachytherapy, 25 systemic therapy). For the other patients, 45 continued to be monitored and their PSA levels continued to increase, and 17 were lost to follow-up after imaging. One patient presented with a false-positive PSA measurement caused by Human Antimouse Antibody.

In 6 patients, choline uptake was deemed false positive based on negative biopsies (n=2), decline of PSA to an undetectable level despite lack of treatment to that site (n=1), histopathologic confirmation of another malignancy (n=2), or histopathologic evidence of inflammation (n=1).

Patterns of choline-positive recurrence

False-positive lesions and the patient with a false-positive PSA measurement were not considered in this analysis. Among the other patients (**Table 3**), choline PET/CT revealed pelvic LN metastases in 48%. The pelvis was the most common site of recurrence after RP, after RP+RT, and also for patients with a persistently elevated PSA level after local therapy. Local recurrence in the prostate bed, identified in 20.3% of patients, was the most common site of recurrence in patients post RT. In 27.6% of patients, PET/CT showed recurrence outside the initial treatment field, mainly in perirectal, presacral, and retroperitoneal LN, or in bone (**Fig. 5 and Supplemental Figs. 1-3)**.

DISCUSSION

This study showed an overall positivity rate of 66% for localizing recurrent PCa when both definitive and equivocal scans were considered positive, *with the rationale that all patients were known to have biochemical recurrence*. This approach yielded a detection rate similar to or slightly higher than rates reported in previous publications (*10, 11, 21, 22*). For instance, in a meta-analysis

of 2,126 patients across 18 studies, the pooled detection rate of ^{11}C-choline for PCa recurrence was 62% (*21*). When considering equivocal scans as negative, we observed a lower detection rate (54%). This is an unlikely low detection rate, as it implies that all equivocal scans would have been false-positives. It is conceivable that the accurate detection rate is between 54–66%, considering that at least some of the equivocal findings (e.g., mild choline uptake in small pelvic nodes) represented early recurrences. It is important to establish a standardized terminology for reporting choline-PET/CT because otherwise some referring physicians may simply dismiss equivocal scan findings as negative, instead of considering them as findings that are suspicious enough to require attention on follow-up. Publications describing choline PET/CT for suspected PCa recurrence remain heterogeneous, largely due to variable inclusion criteria, reading methods and cohort sizes (*11, 21, 23, 24*).

Our multivariate analysis showed that the PSA level at the time of PET imaging was the most crucial parameter to predict scan positivity, in line with other studies (*11*). In univariate analysis, higher Gleason score, higher PSA velocity, persistently elevated PSA after initial treatment, and initial treatment with RT increased the probability for positive choline scans (*10, 25, 26*). Higher scan positivity rates among patients after initial RT are probably explained by the higher PSA levels in this cohort (**Table 3**). This was similarly observed by others (*24, 26*) and, at least in part, may be related to the current definition of recurrence after RT.

The interpretation of choline PET/CT scans poses some unique challenges, particularly compared to PSMA PET/CT, because of the relatively high background activity, low target-to-background activity ratios, and relatively high image noise levels (*13, 15-17*). This is reflected in our lower inter-observer agreement for sites with equivocal focal choline uptake. Depending on whether readers emphasize sensitivity or specificity, and likely also based on their prior

experience, assigning probability scores to sites of focal choline uptake will vary. Thus, in a realistic clinical setting, readers must be aware of all clinical and laboratory data, providing a certain pre-test probability, as well as the numerous reasons for choline uptake unrelated to prostate cancer (*27-29*). For these reasons, in most other studies evaluating the utility of PET/CT in recurrent PCa, readers were aware of clinical data or at least PSA level at the time of imaging, because it is well known (and reproduced in our multivariate analysis) that the probability for a positive scan increases when PSA levels rise.

Analyzing patterns of recurrence may help to understand how choline PET/CT could affect the choice of treatment for recurrent PCa (*20, 30*) **(Supplemental Table 4)**. The patterns observed in our study were generally concordant with those reported previously (*31*). For instance, pelvic LNs were the most common site of recurrence after initial RP. For these patients, the detection of all involved nodes is particularly important and may lead to extending the standard RT field or, conversely, focal dose escalation if no disease outside the prostate bed is found (*20*). Pattern analysis also suggested that standard pelvic dissection may miss nodal metastases, emphasizing the need for better presurgical and/or intraoperative staging with modern imaging tests. Unfortunately, both choline (*8, 32*) and more recently also PSMA (*33-35*) remain suboptimal for this purpose.

PSMA PET imaging is gaining increasing recognition for its ability to detect recurrent PCa. Therefore, we also compared our results with data from some of the largest PSMA studies and meta-analyses in patients with biochemical recurrence (*31, 36-39*). Similar to the literature on choline PET, studies on the utility of PSMA PET in recurrent PCa are heterogenous, applying variable methods: in some studies, multiple independent reader were aware only of the initial treatment and the PSA level at the time of scan, and a majority vote was used in cases of

interobserver disagreements (37); in other studies, multiple physicians classified scan findings during an interdisciplinary conference, with readers aware of clinical data (and possibly prior imaging studies) (36). Recent meta-analyses of PSMA in recurrent PCa (*31,39*) reported slightly lower detection rates than those published before (*38*), reflecting a general trend after the introduction of novel radiotracers (as well as other tests): as experience grows and verification becomes more rigorous, initially high sensitivity and specificity tend to decline to more realistic levels. For instance, similar to choline, there are many potential reasons for nonspecific and false positive PSMA uptake (*40*). Regardless, our results are in line with those from other studies in recurrent PCa, showing that scan positivity with choline is generally lower than that reported for PSMA (ranging from 70.2 to 79.5% (*31, 36-39*)). However, differences were not as striking among patients with low PSA levels, as had previously been suggested (*31, 37-39*) (**Fig. 3)**.

Like almost all previous studies in recurrent PCa, we focused on scan positivity rates. Since the majority of positive findings cannot be confirmed by biopsies due to practical limitations (e.g., multiple suspicious foci, difficulty accessing sites of suspected disease, insufficient tissue samples), we employed the same composite standard of reference generally accepted in this field.

CONCLUSION

^{11}C-choline PET/CT can detect PCa recurrence even among patients with low PSA level when the exam is interpreted by readers aware of the clinical context providing a pre-test probability.

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DISCLOSURE

H. Schoder served as a consultant to Aileron Therapeutics until June 2018 (outside the submitted work). W. Weber serves on advisory boards for and receives compensation from Bayer, Blue Earth Diagnostics, Endocyte, and PentixaPharm. He has received research support from Bristol-Myers Squibb, ImaginAb, Ipsen, and Piramal. M. Morris is an uncompensated consultant for Bayer and Endocyte and a compensated consultant for Advanced Accelerator Applications, Blue Earth Diagnostics, Tokai, Tolmar, and Oric. His research is supported by institutional funds from Bayer, Sanofi, Endocyte, Progenics, Corcept, and Roche, and he has received travel support from Bayer and Endocyte. J. Durack has a patent for biopsy quality assessment technology. He serves as the Chair of the Society of Interventional Radiology Foundation. MSK has received funding from Progenics Pharmaceuticals for an imaging-biopsy correlation study.

KEY POINTS

QUESTION:

Can choline PET/CT still provide clinical utility in prostate cancer recurrence?

PERTINENT FINDINGS:

In retrospective analysis of 287 ^{11}C-choline PET/CT performed to detect recurrent prostate cancer after initial surgery or radiation therapy, the overall positivity rate was 66% when both definitive and equivocal scans were considered positive; when sorted by PSA level, for patients with PSA values of <0.5ng/mL, 0.5–0.99 ng/mL, 1.0–1.99 ng/mL, and ≥2.0 ng/mL, choline PET/CT positivity was 45%, 56%, 70%, and 90.5%. This detection rate is lower than data reported for PSMA PET but among patients with low PSA, differences were not as striking as previously suggested.

IMPLICATIONS FOR PATIENT CARE:

Until PSMA agents are fully approved for PCa, choline PET/CT maintains utility for detecting PCa recurrence even among patients with low PSA levels and may affect the choice of treatment.

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FIGURES

Figure 1. Consort diagram.

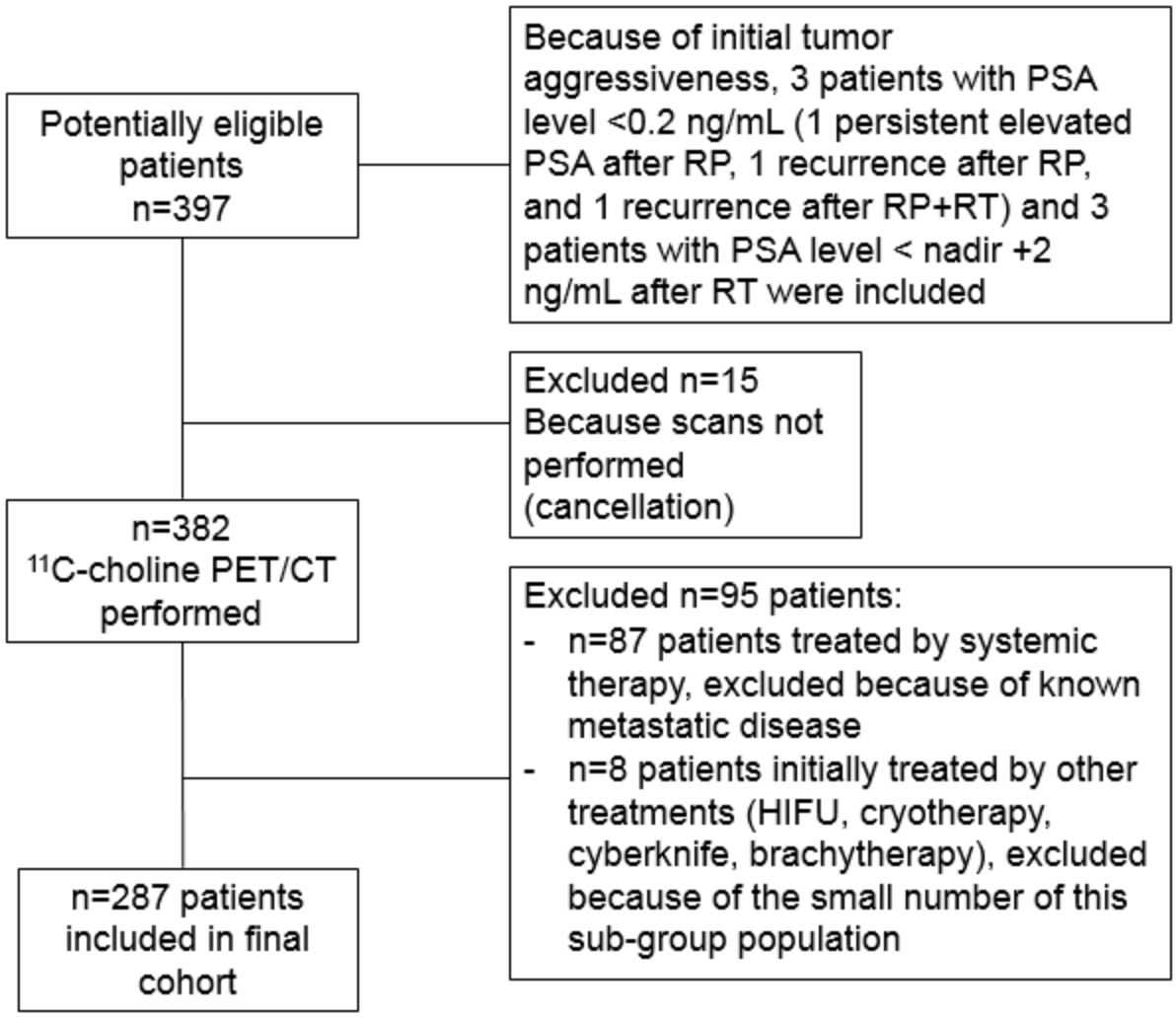
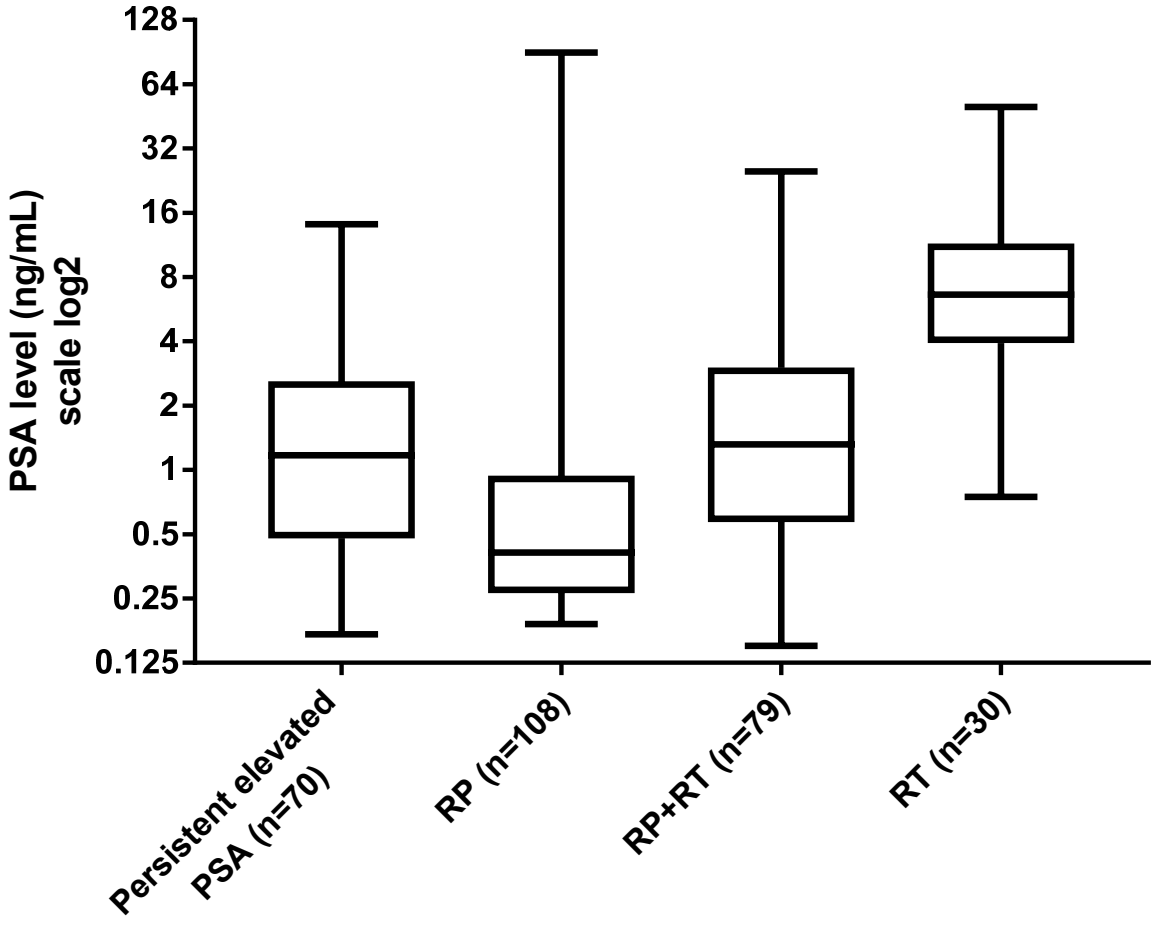


Figure 2. PSA level box plots.



(Boxes contain data between the 25th and 75th percentiles [interquartile range]; whiskers extend from minimum to maximum; horizontal line within box indicates median.

Figure 3. Comparison of our detection rates and published PSMA data. DR=overall detection rate.

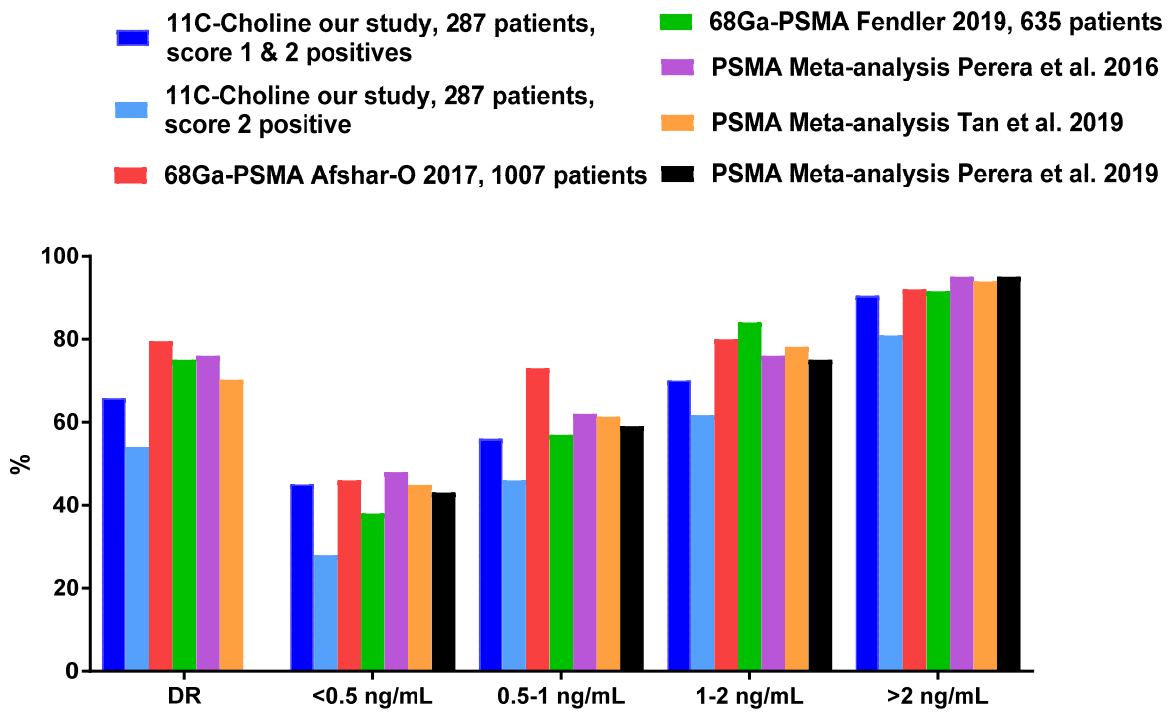
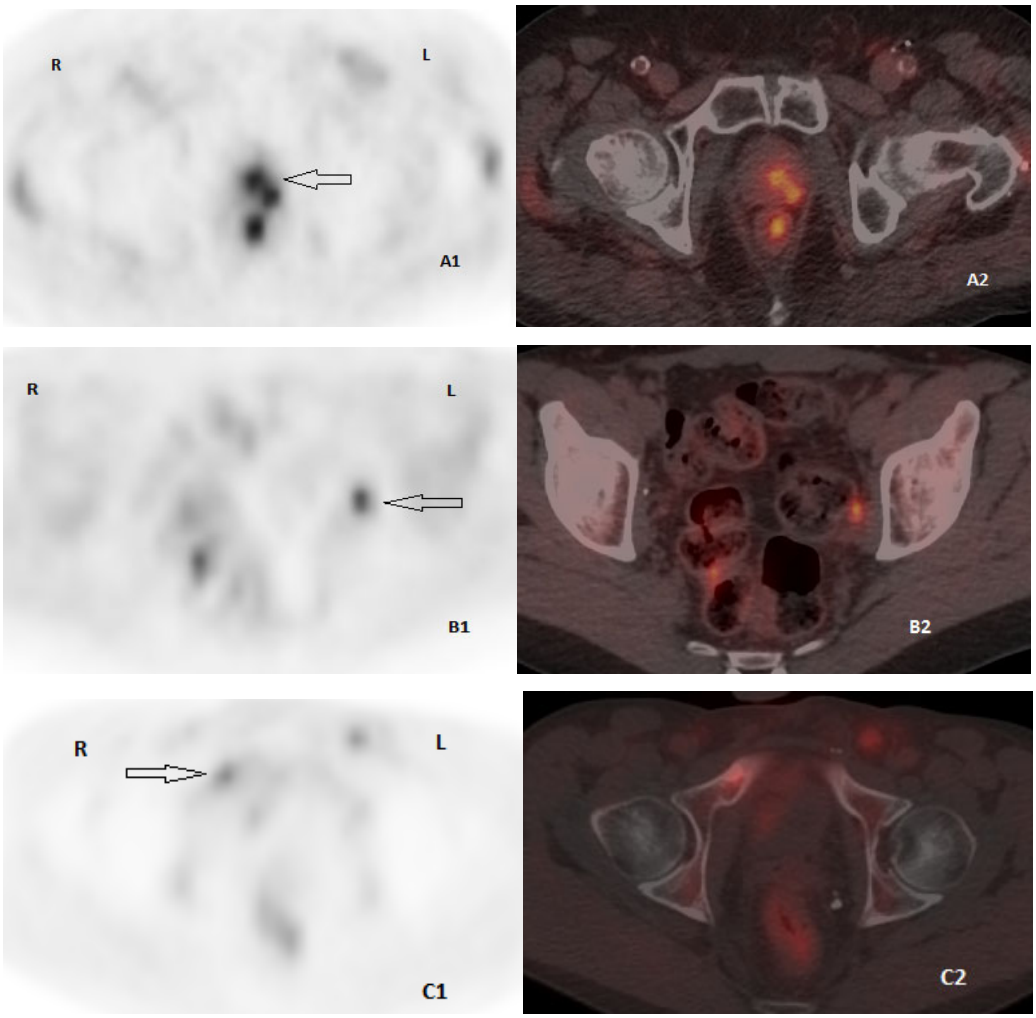
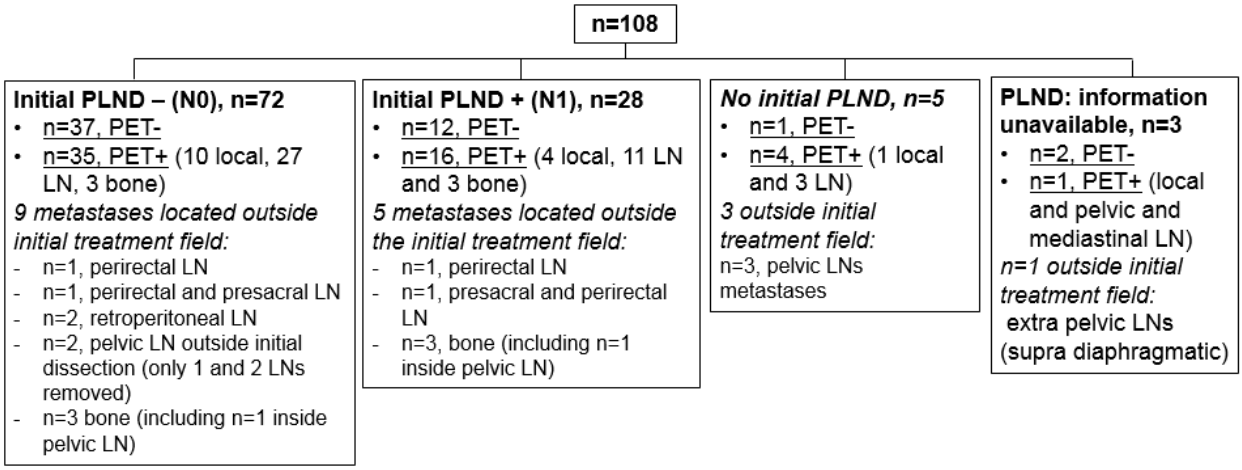


Figure 4. Patient examples.



Pelvic axial PET and PET/CT images: **(A)** PCa 4.3 yrs after IMRT (Gleason 7(4+3),T2cN0M0). PSA=2.28 ng/mL. PET/CT: suspicious prostatic uptake left posterior (SUVmax 3.3) scored 2 (arrow). Local biopsy positive. **(B)** PCa 6.4 yrs after RP+PLND (Gleason 8(4+4),pT2bN0M0). PSA=0.48 ng/mL. PET/CT: suspicious focal uptake (SUVmax 4.5) in non-enlarged left obturator LN, scored 2 (arrow). Histology: positive. **(C)** PCa 10 months after RP+PLND (Gleason 8(4+4),pT4N1M0). PSA=0.46 ng/mL (PSAdt=2.1 months). PET/CT: two suspicious bone foci: right pubic ramus (SUVmax 3) w/sclerotic lesion on CT; posterior 8th rib (not shown) scored 2. Right pubic ramus biopsy: positive.

Figure 5. Patients after initial RP with PET/CT-positive recurrence outside initial treatment field.



TABLES

Table 1. Patient characteristics

Characteristic	N(%) or median (range)
Mean age (years)	67(42-89)
Initial Gleason score:	
6	12(4%)
7	169(59%)
3+4	*91*
4+3	*77*
Unknown	*1*
8	45(16%)
4+4	*43*
3+5	*2*
9	58(20%)
4+5	*53*
5+4	*5*
10	1(0.4%)
unknown	2
NCCN stage	
I	2(1%)
IIA	49(18%)
IIB	36(13%)
III	98(36%)
IV	87(32%)
unknown	15
Initial treatment	
a) Persistent elevated PSA after RP or RT	70(24%)
b) Rising PSA after initially successful surgery or RT:	108(38%)
RP	79(28%)
RP+RT	30(10%)
RT	
Time between initial treatment and ^{11}C-choline PET/CT (years)	4.6(0.2-23.3)

Table 2. ^{11}C-Choline PET/CT findings compared to histology results

Sites	TP	FP	TN	FN
Local	13	4 N=2: MRI suggesting local recurrence, PSA<0.05 after salvage RT+/-HT (biopsy FN?); N=1 w/biopsy planned but not performed for medical reasons	3	2
Pelvic LN	24	2 N=1: perirectal LN (possibly FN biopsy; remained on later PSMA PET after salvage pelvis LND and PSA still elevated); N=1 FP PSA measurement	7	1
Bone	9	3 N=1 myeloma, N=1 benign acetabular lesion, N=1 w/later imaging positive for bone metastases (possibly FN biopsy)	2	0
Extra pelvic LN	1	0	1	0
Lung	1	0	3 (N=1 lung primary; N=2 inflammatory nodules)	0
Neural	1 (neural foramen)	0	0	0

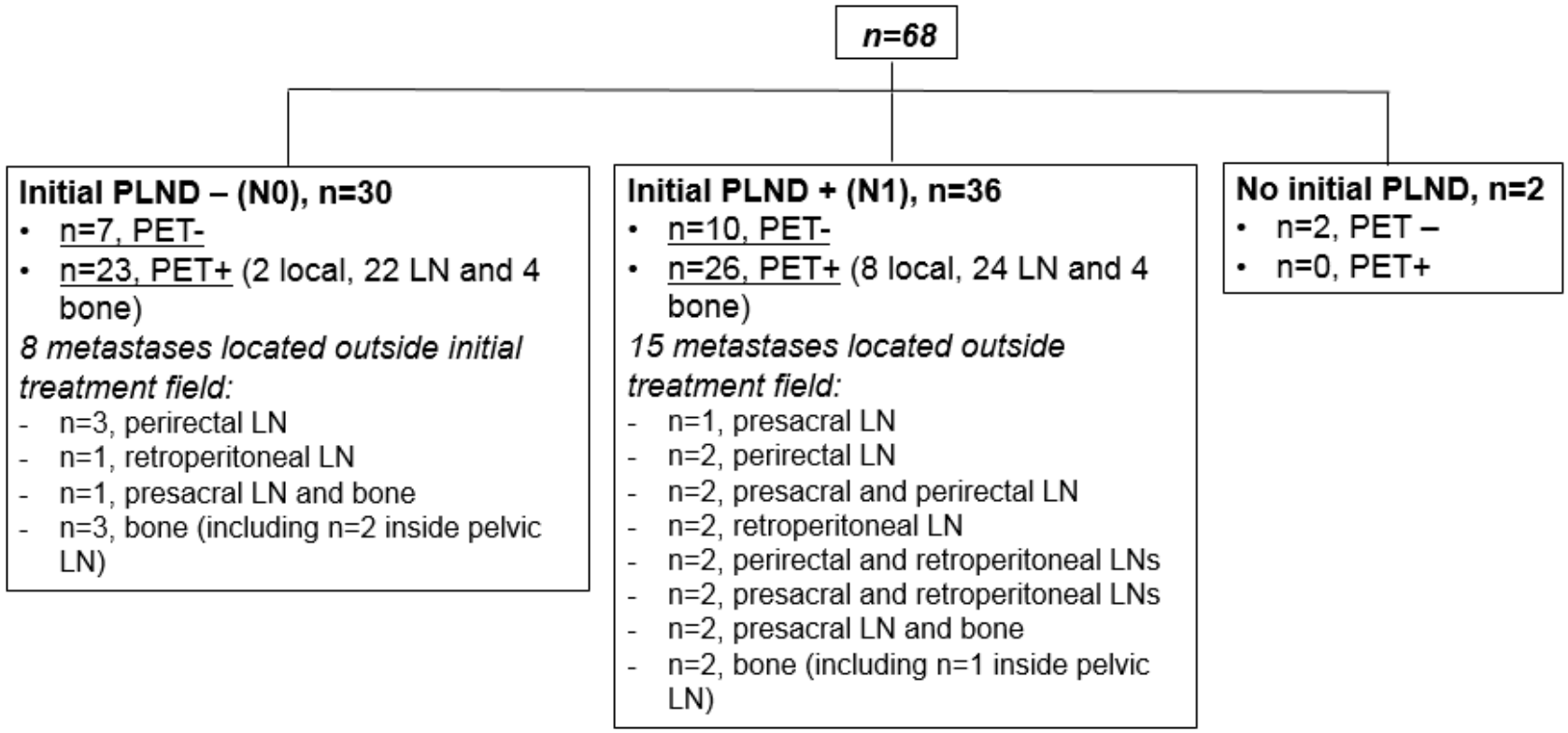
67 patients and 77 sites were biopsied. Of the 67 patients, 49 had at least one PCa-positive biopsy site. TP=true-positive, FP=false-positive, TN=true-negative, FN=false-negative.

Table 3. ^{11}C-choline PET/CT patterns of recurrence

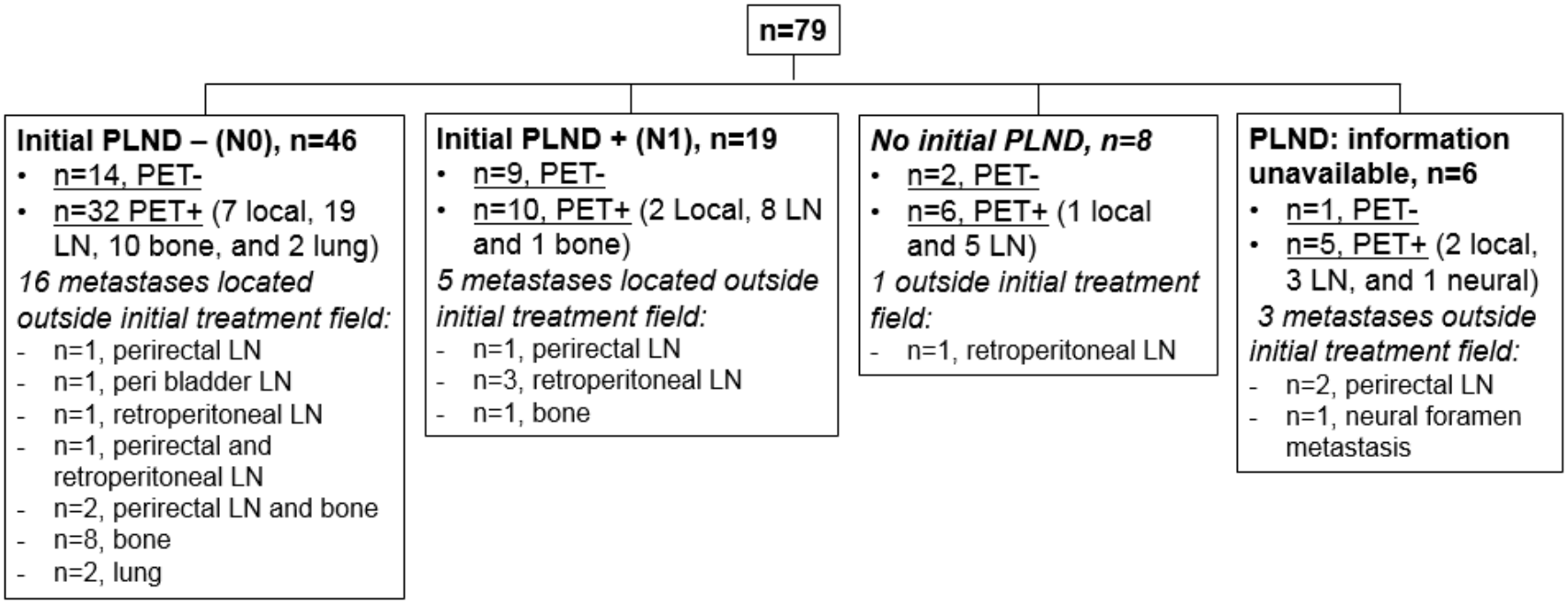
	Persistently elevated PSA	PSA relapse post-RP	PSA relapse post-RP+RT	PSA relapse post-RT
N	**69**	**108**	**79**	**30**
PSA level (ng/mL)	2.1 (0.17-14.13)	2.6 (0.19-89.91)	2.8 (0.15-24.98)	11.3 (0.75-50.15)
PCa Choline PET/CT positivity	50(72.5%)	56(52%)	53(67%)	27(90%)
T+	11(16%)	16(15%)	12(15%)	19(63.5%)
N1	47(68%)	42(39%)	34(43%)	15(50%)
M1a	3(4.5%)	4(3.5%)	7(9%)	3(10%)
M1b	8(11.5%)	6(5%)	11(14%)	5(17%)
M1c	0	0	3(4%)	1(3.5%)
T+N0M0	1(1.5%)	10(9.5%)	6(7.5%)	10(33.5%)
T0N1M0	32(46.5%)	32(29.5%)	22(28%)	5(16.5%)
T+N1M0	6(8.5%)	4(3.5%)	5(6.5%)	3(10%)
T+N0M1	2(3%)	0	1(1.5%)	1(3.5%)
T0N0M1	0	4(4%)	12(15%)	1(3.5%)
T0N1M1	7(10%)	4(3.5%)	7(9%)	2(6.5%)
T+N1M1	2(3%)	2(2%)	0	5(16.5%)
Recurrence outside of initial treatment field	23(33.5%)	18(17%)	25(32%)	13(43.5%)

SUPPLEMENTAL MATERIALS

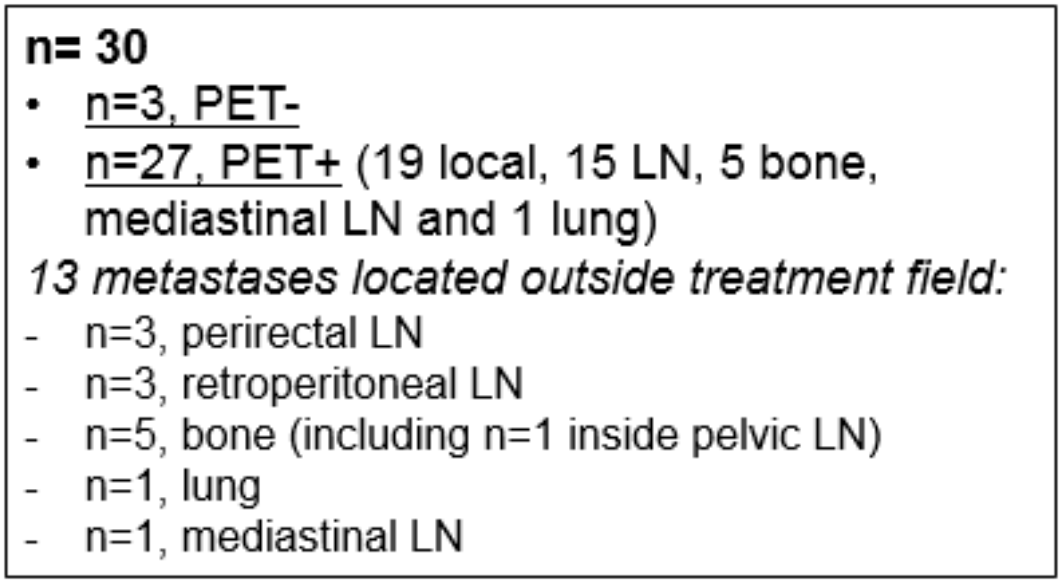
Supplemental Figure 1. Patients with persistently elevated PSA after initial RP and with PET/CT-positive recurrence outside initial treatment field.



Supplemental Figure 2. Patients after initial RP followed by salvage RT with PET/CT-positive recurrence outside initial treatment field.



Supplemental Figure 3. Patients after initial RT with PET/CT-positive recurrence outside initial treatment field.



Supplemental Table 1. ^{11}C-choline PET/CT reading concordance: blinded reading by R1 vs. unblinded reading by R1 and unblinded reading by R1 vs. consensus reading

Unblinded	**Blinded**			**Consensus**			**Total**
Score	**0**	**1**	**2**	**0**	**1**	**2**	
0	83	4	0	80	4	3	87
1	4	33	10	15	23	9	47
2	3	3	147	3	7	143	153
Total	90	40	157	98	34	155	287

The unblinded reading by R1 positivity agreed with the blinded one in 91.6% of cases overall and in 93.8%, 75.9%, and 94.8% for scores 0, 1, and 2, respectively. The *kappa* coefficient was 0.86, while the weighted *kappa* was 0.93.

The consensus reading positivity agreed with the unblinded reading by R1 one in 85.7% of cases overall and in 86.5%, 56.8%, and 92.9% for scores of 0, 1, and 2, respectively. The *kappa* coefficient was 0.76, while the weighted *kappa* was 0.87.

Supplemental Table 2. Patients classified as negative in the blinded reading and equivocal or positive by the unblinded or consensus reading.

age	Gleason	TNM	N	category	delay	PSA level	PSA dt	B	UB	C	Comments	Treatment and follow up
63	9 (4+5)	pT3bN0	III	PSA still high after RP	0.44	0.25	-	0	0	2	Faint uptake in small pelvic LNs not seen by the first reader	Salvage RT, after PSA<0.05ng/mL
66	8 (4+4)	pT3bN1	IV	PSA still high after RP	0.41	2.7	-	0	1	1	After unblinded, small right int iliac LN with faint uptake doubtful because of PSA level and N1	Salvage RT+HT, PSA decreased after therapy
62	7 (4+3)	pT3aN0M0	III	RP+RT	2.20	3.6	0.8	0	0	1	Consensus: doubtful faint pelvic uptake (PSA level)	HT, PSA continue to increase, 4 months after PSA=23.5, new imaging: bone metastasis. Treatment: Olaparib
55	7 (3+4)	pT3aN0	III	RP+RT	5.04	0.25	10.5	0	0	1	Small LN left ext iliac with faint uptake consider inflammatory by the first reader and doubtful after consensus	Observation. 5 months after PSA=0.43ng/mL. New choline PET: unchanged. Continue observation
68	8 (4+4)	pT3bN1	IV	RP	1.22	0.3	1.7	0	0	1	After consensus, doubtful local recurrence	Salvage RT, after PSA<0.05ng/mL
71	7 (3+4)	pT2bN0	IIA	RP	2.33	0.22	8.67	0	0	1	B and UB: T12 right mild uptake without CT correlation, negative in NAC images, seems unspecific. After consensus T12 bone lesion consider as doubtful	Salvage RT pelvic only (T12 not included), after PSA<0.05ng/mL ➔ False positive consensus reading
75	7 (3+4)	pT3aN0	III	RP	11.44	0.6	29.7	0	0	2	B and UB: Iliac distal LNs most likely inflammatory: bilat, fat center and uptake decrease between dynamic, static and final images. After consensus, LNs considered positive because of the PSA level	Salvage RT, after PSA<0.05ng/mL

70	6 (3+3)	pT2bR0N0	IIA	RP	16.98	0.5	6	0	2	2	After unblinded (PSA level and dt): left pararectal LN with mild uptake SUV 1.5 suspicious	biopsy LN para rectal left: positive. Treatment: RT+HT, after PSA< 0.05
75	7 (3+4)	pT2cN0	IIB	RP+RT	17.11	0.6	16.6	0	1	2	After unblinded: mild doubtful local uptake corresponding to the local equivocal nodule described on MRI. After consensus, local uptake considered as suspicious	Follow up because of co-morbidities
68	9 (4+5)	pT2bN0	IIB	RP	0.66	0.3	1.9	0	2	2	After unblinded (Gleason, delay between surgery and rising PSA and PSA dt) suspicious LNs right ext iliac SUVmax 2.3 and right common iliac	Salvage RT+HT, after PSA< 0.05
69	10 (5+5)	pT3bN1	IV	RP+RT	7.80	2.2	4.4	0	1	1	After unblinded (initial Gleason, N1 and PSA level and dt): right ext iliac LN initially considered as inflammatory considered as doubtful	HT
76	7 (3+4)	?	?	RP+RT	15.72	10.4	11	0	1	0	After unblinded (high PSA level) small LNs left obturator and ext iliac SUVmax 1.1 initially considered as inflammatory considered as doubtful. Finally considered inflammatory after consensus	HT
70	7 (4+3)	pT3aN0	III	RP	4.56	0.7	1.4	0	0	2	B and UB: reactive inguinal and ext iliac distal LNs After consensus: ext iliac and RP LNs suspicious because PSA level	Salvage RT+HT, after PSA< 0.05
82	7 (4+3)	maxT2b	IIA	RT	4.76	10.7	9.4	0	2	2	B: pulmonary nodule linked with other disease After unblinded: mild avid lung nodule suspicious in the context (PSA high and no other avidity)	HT

N= NCCN grade; delay= time between initial treatment and PET (years); PSA level ng/mL; PSAdt= PSA doubling time in months; Scores for B= blinded reading, UB= unblinded reading, C=consensus reading; LN= lymph node.

Supplemental Table 3. Correlation between ^{11}C-choline PET/CT positivity and clinical findings (scores 1 and 2 considered positive)

Factors	N	OR	95% CI	Univariate p-value
Gleason score	285			0.24
6-7		Ref.		
8		1.48	0.74, 3.10	
9-10		1.62	0.86, 3.16	
NCCN	272			0.78
I-II		Ref.		
III		0.98	0.53, 1.81	
IV		0.82	0.43, 1.53	
Log(PSA)	287	2.21	1.73, 2.90	**<0.001**
Log(PSA DT)	209	1.27	0.93, 1.75	**0.13**
Log(PSA velocity)	209	1.54	1.24, 1.94	**<0.001**
Log(Time) *	286	0.81	0.59, 1.08	**0.17**
Log(Time)^2 *	286	1.16	0.98, 1.37	**0.08**
Initial treatment	208			**<0.001**
RP		Ref.		
RT		12.5	3.52, 80.0	
Persistently elevated PSA		2.40	1.27, 4.67	

* LogTime and LogTime squared are analyzed together in the same model. In univariate analysis, increasing log(PSA) value, increasing log(velocity), as well as RT treatment and persistently elevated PSA are associated with a higher risk of scan positivity.

Variables with a p-value <0.20 in univariate analysis were entered in the multivariate model.

When adjusted for the other variables, only the value of log(PSA) was associated with the risk of having a positive scan: OR = 2.21 (95% CI 1.73, 2.90; p<0.001).

Supplemental Table 4. Examples of patients for whom ^{11}C-choline PET had an impact on management

age	Gleason	TNM	N	category	delay	PSA level	PSA dt	B	UB	C	11C-Choline findings	Other prior imaging findings	Treatment and follow up
63	9 (4+5)	pT3bR0N0M0	III	PSA still high after RP	0.38	2.23	-	2	2	2	LN metastases left pre-sacral (SUVmax 6.7) and 4th rib uptake (SUVmax 8.5) highly suspicious of bone metastasis	Pelvic MRI and bone scintigraphy negative	Rib biopsy: positive for PCa metastasis Treatment: HT
73	7 (4+3)	pT3aN1M0	IV	PSA still high after RP	0.26	0.35	-	2	2	2	Small LN right para rectal (SUVmax 1.3), positive on NAC images, suspicious of metastasis	Pelvic MRI: no recurrence	Modification of the RT field including pararectal area. Treatment: RT (prostatic bed and nodes), then PSA<0.05
70	9(4+5)	pT3aN1M0	IV	RP+RT	1.88	1.11	0.6	2	2	2	T5 bone metastasis left anterior (SUVmax 6.6)	CT and bone scintigraphy: negative	Bone MRI: T5 suspicious T5 biopsy: positive for PCa metastasis Treatment: T5 RT and HT, after PSA<0.05
58	7 (3+4)	pT3bN0M0	III	RP	7.80	0.2	11.62	2	2	2	LN metastatic right internal iliac (SUVmax 2.4)	Pelvic MRI and bone scintigraphy negative	Right int iliac LN dissection: positive.
59	7(4+3)	?	?	RT	3.31	47.32	4.1	2	2	2	Local recurrence (SUVmax 4.8) and LN metastasis: obturator, external iliac, common iliac (left: SUVmax 15), peri aortic and infra mediastinal posterior	Chest-abdomen-pelvis CT: no evidence of metastatic disease	Treatment: HT

N= NCCN grade; delay= time between initial treatment and PET (years); PSA level ng/mL; PSA dt = PSA doubling time in months; Scores for

B= blinded reading, UB= unblinded reading, C=consensus reading, LN= lymph node, ?=unknown.