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^{68}Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0ng/ml: Impact on Salvage Radiotherapy Planning

Jeremie Calais[1], Johannes Czernin[1], Minsong Cao[2], Amar U. Kishan[2], John V. Hegde[2], Narek Shaverdian[2], Kiri Sandler[2], Fang-I Chu[2], Chris R. King[2], Michael L. Steinberg[2], Isabel Rauscher[3], Nina-Sophie Schmidt-Hegemann[4], Thorsten Poeppel[5], Philipp Hetkamp[5], Francesco Ceci[1], Ken Herrmann[1,5], Wolfgang P. Fendler[1,6], Matthias Eiber[1,3], Nicholas G. Nickols[2,7]

[1]Ahmanson Translational Imaging Division, Department of Molecular and Medical Pharmacology, UCLA, Los Angeles, CA, USA
[2]Department of Radiation Oncology, UCLA, Los Angeles, CA, USA
[3]Department of Nuclear Medicine, Klinikum rechts der Isar, Technical University of Munich, Germany
[4]Department of Radiation Oncology, University Hospital, LMU Munich, Germany
[5]Department of Nuclear Medicine, Universitätsklinikum Essen, Germany
[6]Department of Nuclear Medicine, Ludwig-Maximilians-University Munich, Germany
[7]Department of Radiation Oncology, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

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Corresponding author:
Dr Jeremie Calais
Ahmanson Translational Imaging Division
UCLA Nuclear Medicine Department
200 Medical Plaza, Suite B114
Los Angeles, CA 90095-7370
TEL (310) 825-3617
FAX (310) 206-4899
EMAIL JCalais@mednet.ucla.edu

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ABSTRACT

Background: Target volume delineations for prostate cancer (PCa) salvage radiotherapy (SRT) after radical prostatectomy are usually drawn in the absence of visibly recurrent disease. Gallium-68 Prostate Specific Membrane Antigen Positron Emission Tomography/Computed Tomography (^{68}Ga-PSMA-11 PET/CT) detects recurrent PCa with sensitivity superior to standard of care imaging at serum prostate specific antigen (PSA) values low enough to impact target volume delineations for routine SRT. **Objective**: To i) map the recurrence pattern of PCa early biochemical recurrence (BCR) after radical prostatectomy with ^{68}Ga-PSMA-11 PET/CT in patients with serum PSA levels <1 ng/ml, ii) determine how often consensus clinical target volumes (CTV) based on the Radiation Therapy Oncology Group (RTOG) guidelines cover ^{68}Ga-PSMA-11 PET/CT-defined disease, and iii) assess the potential impact of ^{68}Ga-PSMA-11 PET/CT on SRT. **Patients and Methods:** This is a post-hoc analysis of an intention-to-treat population of 270 patients who underwent ^{68}Ga-PSMA-11 PET/CT at 4 institutions for BCR after prostatectomy without prior radiotherapy at PSA<1 ng/mL. RTOG consensus CTV that included both the prostate bed and pelvic lymph nodes were contoured on the CT dataset of the PET/CT by a radiation oncologist blinded to the PET component. ^{68}Ga-PSMA-11 PET/CT images were analyzed by a nuclear medicine physician. PSMA-positive lesions not covered by planning volumes based on the consensus CTV were considered to have a major potential impact on treatment planning. **Results:** The median PSA at the time of ^{68}Ga-PSMA-11 PET/CT was 0.48 ng/ml (range 0.03-1). One-hundred-thirty-two/270 patients (49%) had a positive ^{68}Ga-PSMA-11 PET/CT. Fifty-two/270 (19%) had at least one PSMA-positive lesion not covered by the consensus CTV. Thirty-three/270 (12%) had

extra-pelvic PSMA-positive lesions and 19/270 (7%) had PSMA-positive lesions within the pelvis but not covered by consensus CTV. The two most common ^{68}Ga-PSMA-11 PET-positive lesion locations outside the consensus CTV were bone (23/52, 44%) and perirectal lymph nodes (16/52, 31%). **Conclusion:** Post-hoc analysis of ^{68}Ga-PSMA-11 PET/CT implies a major impact on SRT planning in 52/270 patients (19%) with PCa early BCR (PSA<1.0 ng/ml). This justifies a randomized imaging trial of SRT with or without ^{68}Ga-PSMA-11 PET/CT investigating its potential benefit on clinical outcome.

INTRODUCTION

PCa BCR occurs in 20 to 80% of patients within 10 years after radical prostatectomy, with the risk of failure dependent on National Comprehensive Cancer Network (NCCN) risk group, pathologic features, and genomic classification (*1*,*2*). After BCR, salvage radiation therapy (SRT) is the main curative option (*3*). Overall, SRT offers long-term biochemical control in about 50% of patients (*4*), depending on pre-SRT prostate-specific antigen (PSA) (*5*), RT dose (*6*) and risk group (*7*). For high-risk patients, 5-year BCR after SRT reaches 70% (*8*,*9*). Intuitively, SRT is only curative if recurrent disease is completely encompassed by the irradiated volumes. Therefore, accurate estimation of the location of recurrent disease is critical.

In practice, SRT is commonly initiated in patients with serum PSA levels <1 ng/mL, a threshold at which standard of care imaging is insensitive for detecting recurrence (*10*). As such, SRT target volumes are usually drawn in the absence of radiographically visible disease (gross disease). The RTOG published contouring guidelines for both prostate bed and pelvic lymph node (LN) CTV (areas with potential microscopic occult tumor) based on a consensus panel of experienced genitourinary radiation oncologists (*11*,*12*). These consensus CTV are applied in ongoing clinical trials and guide routine care.

Gallium-68 labelled prostate-specific membrane antigen positron emission tomography (Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)]) (^{68}Ga-PSMA-11 PET/CT) is superior to standard of care imaging for detecting regional and distant metastatic recurrent PCa at low PSA levels (*13–16*), highly specific (*16*) and reproducible (*17*). Detection rates of about 50% are reported even at PSA levels of <0.5 ng/ml (*15*,*16*). Therefore ^{68}Ga-

PSMA-11 PET/CT has the potential to guide and improve target volume delineations for SRT.

The potential impact of ^{68}Ga-PSMA-11 PET/CT on RT planning has been assessed in several inhomogeneous patient groups with primary and recurrent disease. These studies established that ^{68}Ga-PSMA-11 PET/CT can image PCa at low serum PSA values and potentially impact radiotherapy planning. Limitations include inconsistent descriptions of anatomic relapse patterns and the pooling of patients with a wide range of serum PSA values and clinical disease states (*18–24*).

We present a large cohort of patients who underwent ^{68}Ga-PSMA-11 PET/CT at a PSA <1 ng/mL after prior prostatectomy. This cohort of patients is representative of those who are routinely offered SRT in the absence of radiographically visible disease. We i) map the ^{68}Ga-PSMA-11 PET/CT recurrence pattern of early BCR after prostatectomy, ii) evaluate how often SRT based on consensus contouring guidelines fails to cover PSMA-expressing disease, and iii) assess the potential impact of ^{68}Ga-PSMA-11 PET/CT on SRT planning for patients with PCa early BCR.

METHODS

Patients and Data Management

We first identified 270 consecutive and well documented patients from databases established at 4 institutions (Technical University of Munich (n=147); University of California Los Angeles (UCLA, n=47; clinicaltrial.gov identifier NCT02940262, Institutional Review Board IRB#16-001095); Ludwig-Maximilians-University of Munich (n=40) and

University of Essen (n=36)). All patients underwent radical prostatectomy, had BCR without prior RT and underwent ^{68}Ga-PSMA-11 PET/CT at a serum PSA level of <1 ng/ml between August 2013 and May 2017 to detect the sites of recurrence. All patients gave written consent to undergo the procedures. Clinical data and DICOM (digital imaging and communications in medicine) files of all patients were anonymized and imported onto a dedicated radiotherapy contouring workstation at UCLA (MIM 6.7.5, MIM software Inc, Cleveland, OH). UCLA IRB approved this anonymized post-hoc retrospective analysis and the requirement to obtain informed consent was waived (IRB#17-001340).

^{68}Ga-PSMA-11 **PET/CT Images Acquisition**

^{68}Ga-PSMA-11 PET/CT imaging was performed according to recent guidelines (*25*). Images were acquired on different PET/CT devices: the Siemens Biograph 128 mCT (n=183, 68%), Siemens Biograph 64 (n=50, 19%), Siemens Biograph 64 mCT (n=24, 9%), or GE Discovery 690 (n=13, 5%). The ^{68}Ga-PSMA-11 compound was used at all sites (*26*). The median injected dose was 154 MBq (range 65-267 MBq). To reduce bladder activity patients received 20 mg of furosemide at the time of tracer injection if there was no contraindication. The median uptake period was 59 min (range 37-132 min). A diagnostic CT scan (200-240 mAs, 120 kV) was performed after intravenous injection of contrast agent (if no contraindication existed) followed by the whole-body PET image acquisition (2-4 min/bed position).

Simulation of Consensus Salvage Radiotherapy Planning

SRT consensus CTV were contoured on the CT dataset of the PET/CT for all 270 patients by an experienced radiation oncologist (NN) who was blinded to the PET findings. Consensus RTOG contouring guidelines were used (*11*,*12*) (Figure 1, Panel A), except that the common iliac nodes were contoured beginning inferior to L4/L5 (rather than L5/S1). Briefly, the prostate bed CTV included the anatomical prostatic fossa and the seminal vesicle remnants. The pelvic nodal CTV included presacral, common iliac, internal iliac, external iliac and obturator LNs. Although the addition of pelvic LN irradiation in SRT is controversial (*27*,*28*) and under investigation (RTOG 0534, NCT00567580), we included pelvic LN coverage along with the prostate bed for all patients to establish a generous estimate of how often SRT based on consensus CTV fails to cover PSMA-expressing recurrent disease.

^{68}Ga-PSMA-11 **PET/CT Image Analysis**

Next, all ^{68}Ga-PSMA-11 PET/CT images were analyzed by an experienced nuclear medicine physician (JC) according to recent recommendations (*25*,*29*): any focal uptake of ^{68}Ga-PSMA-11 above surrounding background and not associated with physiological uptake or known pitfalls (*30*) was considered suspicious for malignancy (Figure 1, Panel B). Distinction between malignant and inflammatory lymph nodes (reactive, granuloma, etc.) was based on degree of PSMA uptake, typically intermediate and low for inflammation, and location, typically peri-hilar, axillary or inguinal for inflammatory nodes. Based on TNM staging the following regions were systematically analyzed for recurrence: prostate bed/ seminal vesicle remnants (T), pelvic lymph nodes (N) (internal Iliac, obturator, external Iliac, perirectal, pre-sacral, common Iliac), extra-pelvic lymph nodes

(M1a) (retro-peritoneal, inguinal, chest, other), bone (M1b) and other visceral organs (M1c).

^{68}Ga-PSMA-11 PET Lesions Contouring

In a third step ^{68}Ga-PSMA-11 PET-positive lesions were contoured (JC) on the CT images (Figure 1, Panel C). These contours were subsequently used to define ^{68}Ga-PSMA-11 PET-based target volumes. Moreover, we generated a 3D map of all ^{68}Ga-PSMA-11 PET-positive lesions contours across the entire study population on a template patient (Figure 2). This was achieved by rigid image registration of each patient's CT to the template patient. Then the ^{68}Ga-PSMA-11 PET-based contours were transferred to the template patient through this registration (MIM 6.7.5, MIM software Inc., Cleveland, OH).

Co-registration of Consensus CTV with ^{68}Ga-PSMA-11 PET/CT Images

In a final step, the consensus CTV were co-registered with the ^{68}Ga-PSMA-11 PET/CT images (Figure 1, Panel D). Contours including the PSMA-positive lesions were then compared with the consensus CTV for each patient to assess whether PSMA-positive lesions were localized inside (Figure 3) or outside (Figure 4) of the consensus CTV. To take into consideration the final planning target volumes (PTVs), only PSMA-positive lesion contours ≥ 10 mm remote from the CTV were considered inadequately covered. As many modern centers utilize CTV to PTV expansions of less than 10 mm, this analysis should yield a generous estimate of the how often planning based on consensus CTV offers adequate coverage. PSMA-positive lesions within either the prostate bed or pelvic LN consensus CTV were considered covered.

Potential Impact of ^{68}Ga-PSMA-11 PET/CT on Radiotherapy Planning

PSMA-positive lesions not covered by the consensus CTV were considered to have a major potential impact on treatment planning. *Major potential impact* was further sub-classified as: extension of the CTV to cover PSMA-positive lesions within the pelvis; superior extension of CTV to cover para-aortic LNs; addition of metastasis-directed stereotactic body radiation therapy (SBRT) for extra-pelvic oligometastatic disease (1-5 extra-pelvic sites that are M1a or M1b); or radiotherapy not indicated (futile) due to the presence of visibly polymetastatic (>5 M1a or M1b) or visceral metastatic disease (M1c). If PSMA-positive lesions were covered by the CTV, the potential impact of ^{68}Ga-PSMA-11 PET/CT on treatment planning was defined as *minor* (potential for dose-escalation to gross disease (visibly PSMA-PET-positive). Negative ^{68}Ga-PSMA-11 PET/CT studies were considered to have no impact on SRT planning.

Statistical Analysis

We performed a post-hoc analysis of this intention to treat population and simulated the impact of ^{68}Ga-PSMA-11 PET/CT on SRT planning. Descriptive statistics were used (median, range). The comparisons for clinical/pathologic characteristics between positive and negative ^{68}Ga-PSMA-11 PET/CT patients were conducted using t-test along with Wilcoxon test as a verification for continuous variables and Chi-squared test for categorical variables. Particularly, the serum PSA level prior PET/CT was considered as the continuous variable first and converted into a categorical variable, low PSA (0.5-1.0 ng/ml) and very low PSA (<0.5 ng/ml) group, for the purpose of comparison. Above analyses were conducted in R (*31*).

RESULTS

Patient Characteristics

Table 1 summarizes clinical and pathologic characteristics of the 270 patients. In brief, median age was 68 years (range 43-90) and the median serum PSA level was 0.44 ng/ml (range 0.03-1). Thirty-three/270 patients (12.5%) had androgen deprivation therapy (ADT) within 6 months prior to the ^{68}Ga-PSMA-11 PET/CT study. Thirty-six/270 (13.5%) were NCCN-defined intermediate-risk. One-hundred-sixty-three/270 (60.5%) were NCCN-defined high-risk, 142/270 (52.5%) were pT3, and 54/270 (20%) were pN1. Sixty-seven/270 patients (25%) had positive surgical margins (R1). Overall, the cohort was at high risk for treatment failure following prostatectomy.

^{68}Ga-PSMA-11 PET/CT Findings and Consensus CTV

Table 2 and Table 3 depict the ^{68}Ga-PSMA-11 PET/CT findings. One-hundred-thirty-two/270 patients (49%) had a positive ^{68}Ga-PSMA-11 PET/CT study. Fifty-two/132 patients (39%) had at least one PSMA-positive lesion not covered by consensus CTV: 33/132 (25%) had extra-pelvic metastases while 19/132 (14%) had PSMA-positive pelvic lesion(s) not covered by consensus CTV without extra-pelvic metastases. The three most common ^{68}Ga-PSMA-11 PET positive lesion locations outside the consensus CTV were bone (23/52, 44%), perirectal LNs (16/52, 31%) and distal external iliac LNs (9/52, 17%). Figure 2 displays a 3D map of all ^{68}Ga-PSMA-11 PET recurrences outside of the consensus CTV co-registered upon a template patient's CT.

^{68}Ga-PSMA-11 PET/CT Findings and Clinical/Pathologic Characteristics

The 132 positive ^{68}Ga-PSMA-11 PET/CT patients had significantly higher PSA levels (median 0.5 vs 0.36 ng/ml; p<0.001) and shorter time to recurrence (median 21.3 vs 30.4 months; p=0.05) than the 138 negative ones. The detection rate (at least one PSMA-positive finding) was significantly higher in patients with Gleason score >7 than in those with Gleason score ≤7 (56/86 (65%) vs 68/168 (40%); p <0.001), in N1 patients than in N0 patients (35/54 (65%) vs 75/166 (45%); p = 0.02) and in T3 patients than in T2 patients (82/144 (57%) vs 34/99 (34%); p < 0.001). One hundred fifty three patients had serum PSA levels of <0.5 ng/mL (very low PSA group) and 117 had levels between 0.5 and 1.0 ng/ml (low PSA group). The detection rate was significantly higher in the low PSA group than in the very low PSA group: (70/117 (60%) vs 62/153 (40.5%); p = 0.003). The frequency of PSMA-positive lesions not covered by the consensus CTV had borderline significant dissimilar pattern in the low and the very low PSA group (29/117 (25%) vs. 23/153 (15%); p = 0.06).

Verification of PSMA-positive Lesions Outside Consensus CTV

Lesions not covered by the consensus CTV were verified in 24/52 patients (46%). This was done by biopsy (n=1), surgery (n=3), bone scan (n=1), magnetic resonance imaging (n=1), follow-up imaging (CT or PET/CT) showing progression at the site (n=8), follow-up imaging (CT or PET/CT) showing response to treatment (n=5) or by observing a decrease in serum PSA after focal treatment (SBRT; n=5), respectively.

Potential Impact of ^{68}Ga-PSMA-11 PET/CT on SRT Planning

Table 4 summarizes the potential impact of ^{68}Ga-PSMA-11 PET/CT on SRT planning.

Potential Major Impact, Fifty-two patients had at least one PSMA-positive lesion not covered by the consensus CTV (19% of all 270 patients, 39% of 132 PSMA-positive patients). SRT based on consensus CTV would not be curative for these patients. Nineteen patients with pelvic LN metastasis outside the consensus CTV (7% of all 270 patients, 14% of 132 PSMA-positive patients) could have experienced extension of consensus CTV to cover PSMA-expressing disease. Twenty-two of the 33 patients with extra-pelvic metastases (67%) were oligometastatic (≤5 metastatic sites), potentially eligible for metastasis-directed stereotactic body radiation therapy (SBRT); 5/33 (15%) could have experienced superior extension of the nodal CTV to encompass the para-aortic LNs, and 6/33 (18%) had visceral or diffuse metastatic disease (3 with multiple lung metastasis and 3 with ≥ 5 metastatic sites), and would be unlikely to benefit from local or metastasis-directed therapy.

Potential Minor Impact, Eighty patients (29.5% of all 270 patients, 61% of 132 PSMA-positive patients) had PSMA-positive lesions covered by the consensus CTV and thus could have experienced focal dose escalation, which is often customary for irradiation of areas known to harbor gross disease.

DISCUSSION

The lack of sensitivity of standard of care imaging for recurrent PCa combined with a sensitive and specific biomarker of early disease recurrence (PSA) generates a unique challenge for local treatment of PCa BCR: we know there is cancer, but we do not know

where it is. There is thus an unmet clinical need to improve target delineation in patients with potentially curable PCa with early BCR.

We report in this post-hoc analysis of 270 patients with early BCR after prostatectomy that ^{68}Ga-PSMA-11 PET/CT would have had a major impact in 19% of patients (39% of PSMA-positive patients) and a minor impact on 30% of patients imaged (61% of PSMA-positive patients). Overall, the addition of ^{68}Ga-PSMA-11 PET/CT may impact SRT planning in half of patients with a PSA <1 ng/mL. Prospective clinical trials are necessary to assess the clinical value of a restaging ^{68}Ga-PSMA-11 PET/CT prior to SRT.

Somewhat encouragingly, despite most patients being high-risk, treatment volumes based on consensus CTV covered all PSMA-positive lesions for 61% of patients with a positive ^{68}Ga-PSMA-11 PET/CT. This frequency is consistent with the historical success rate of SRT. However, consensus CTV were inadequate to cover all PSMA-positive lesions in 39% of patients with a positive ^{68}Ga-PSMA-11 PET/CT.

The detection rate of 49% for PSMA-positive lesions in this cohort with BCR after surgery and a low PSA level (<1.0ng/ml) is consistent with previous reports (*15*,*16*). The anatomical distribution of PSMA-positive lesions is consistent with previous PET studies using choline and PSMA-ligands in the setting of BCR (*9*,*19*,*24*,*32–35*). The most common nodal regions outside of the CTV in patients in this study were the perirectal (n=16), distal external iliac (n=9), and para-aortic (n=5), which are neither assessed by routine lymph node dissections at prostatectomy nor targeted by routine SRT. It is unlikely that a uniform expansion of the consensus CTV to cover these regions would be feasible, given risks for additional toxicity. Notably, most PSMA-positive nodes were sub-centimeter (median LN

short axis: 6 mm (range 3-17)). The vast majority of PSMA-positive lesions in the prostate bed were covered. Furthermore, 32 patients (24% of the 132 PSMA-positive patients) had PSMA-positive lesions isolated to the prostate bed alone, while 67/132 patients (51%) had PSMA-positive lesions within the pelvis but without distant metastasis. This underscores the potential benefit of including pelvic nodal CTV, which is currently under investigation in prospective trials (RTOG 0534, NCT00567580).

Importantly, the most common PSMA-positive lesion locations outside the consensus CTV were bone (23/52, 44%). No expansion of current CTV would successfully cover these recurrences. A majority of M1 patients (67%) in this study were oligometastatic M1a or M1b (1 to 5 extra-pelvic sites). Currently, most patients with M1 PCa receive palliative hormonal therapy as primary treatment. The use of image-guided, metastasis directed ablative therapy (such as SBRT) to distant lesions is an attractive strategy (*35*–*38*) being investigated in prospective trials (NCT01558427, NCT02274779) (*39*,*40*). The success of this approach, however, depends on accurate staging. ^{68}Ga-PSMA-11 PET/CT is probably the most sensitive imaging modality to select patients who might benefit.

The impact of choline PET/CT imaging on SRT planning has been assessed in several retrospective studies (*9*,*32*,*33*,*41*–*45*). Impact ranged from 13.5% to 81.3% with a median rate of 32%. Taken together, these studies found that addition of choline PET/CT to SRT planning changed the initial plan in 357 of 1083 patients (33%). However, ^{68}Ga-PSMA-11 PET/CT is superior to choline PET/CT as shown in several studies (*13*,*46*–*48*) with a more favorable tumor to background ratio and better sensitivity for lesion detection at low PSA values (PSA < 2ng/mL). Therefore a higher impact of ^{68}Ga-PSMA-11 PET/CT

on SRT planning would be expected. Several prior studies did report on the potential impact of ^{68}Ga-PSMA-11 PET/CT imaging on RT planning (*18–22*,*24*,*35*). Impact ranged from 34 to 87% with a median rate of 57%. However limitations were inhomogeneous patient groups with primary and recurrent disease, a wide range of serum PSA values and clinical disease states (*18–24*). Therefore, strengths unique to our study include its large size (270 patients), that all patients had BCR following radical prostatectomy without prior RT, and that all patients had PSA<1 ng/mL at the time of ^{68}Ga-PSMA-11 PET/CT imaging. This is the most relevant patient cohort to assess the impact of ^{68}Ga-PSMA-11 PET/CT on SRT.

Limitations

This is a post-hoc retrospective analysis of a well-controlled patient cohort. The design of this study precludes analysis of the impact of ^{68}Ga-PSMA-11 PET/CT on clinical outcomes. To minimize bias, consensus CTV were drawn blind to the ^{68}Ga-PSMA-11 PET images. Another limitation is the absence of lesion verification in all patients, but lesion confirmation in recurrent patients is frequently not feasible.

CONCLUSION

This multicenter study post-hoc analysis of 270 patients with PCa early BCR (PSA<1.0 ng/ml) following radical prostatectomy implies a major impact (19%) of ^{68}Ga-PSMA-11 PET/CT on SRT. This justifies a randomized prospective trial to determine whether ^{68}Ga-PSMA-11 PET/CT can improve outcomes in patients with PCa early BCR following radical prostatectomy.

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FIGURES LEGENDS

Figure 1: Methodology. First, consensus RTOG CTV were contoured on the CT dataset of the PET/CT for all 270 patients by an experienced radiation oncologist who was blinded to the PET findings as seen on Panel A (Prostate bed CTV in orange and pelvic lymph nodes CTV in green). Second, all ^{68}Ga-PSMA-11 PET/CT images were analyzed by an experienced nuclear medicine physician (Panel B). Third, PSMA-positive lesions were contoured in yellow on the CT images (Panel C). Fourth, the consensus CTV were co-registered with the ^{68}Ga-PSMA-11 PET/CT images and the PSMA-positive lesions contours (yellow) to assess for each patient whether PSMA-positive lesions were localized inside or outside of the consensus CTV (Panel D).

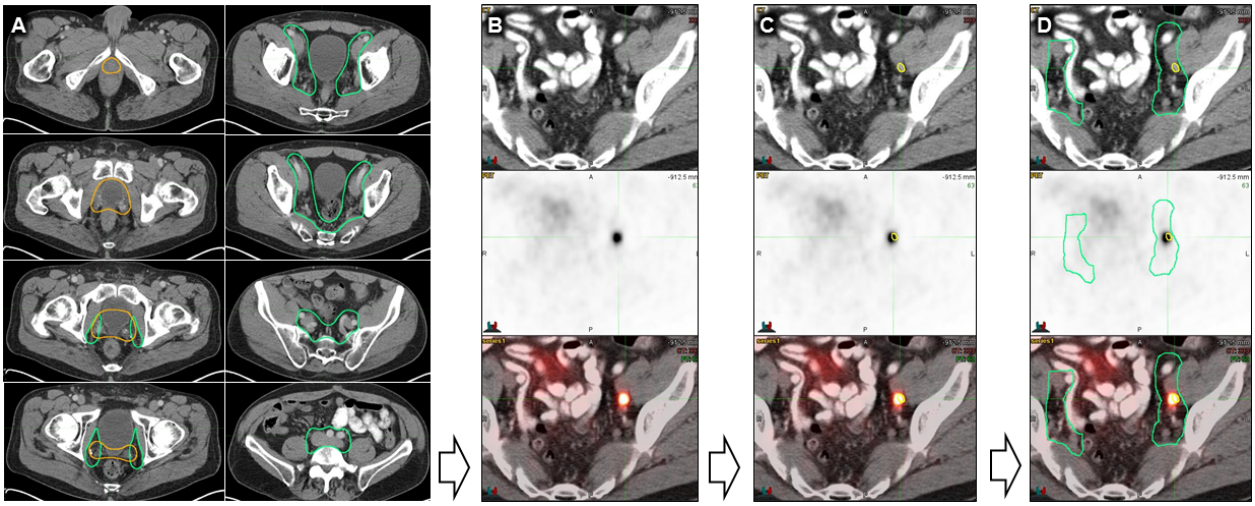


Figure 2: 3D map rendering of all PSMA-positive lesions (yellow) of the 52 patients with recurrences outside of the consensus target volumes (23 patients with recurrences outside only and 29 patients with recurrences outside and inside the target volumes). This was achieved by rigid image registration of each patient CT to a template patient CT then followed by the transfer of each PSMA-positive lesion contour on the template patient CT (MIM 6.7.5, MIM software Inc., Cleveland, OH). On the right side are shown the 3D prostate bed consensus target volume in orange and the 3D pelvic lymph node consensus target volume in green.

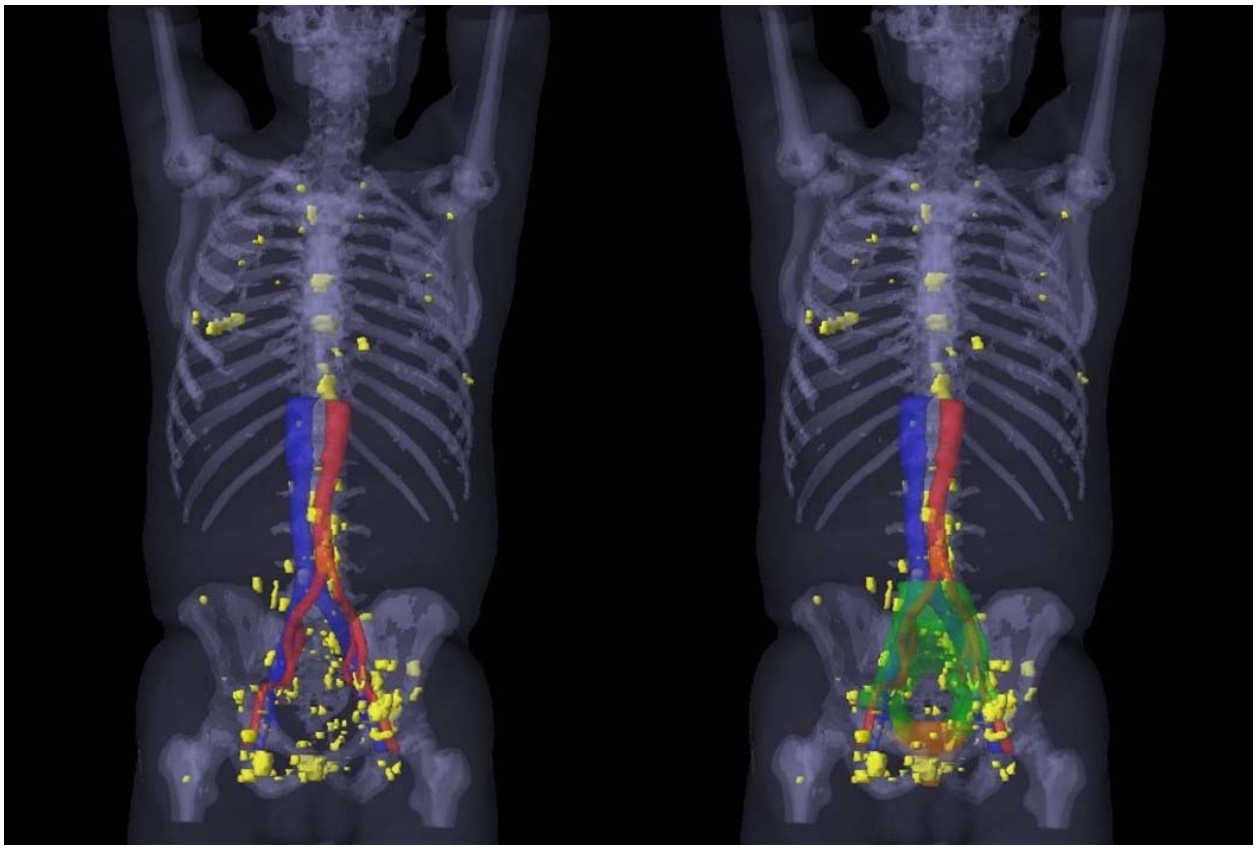


Figure 3: PSMA-positive lesions (contours in yellow) situated inside the prostate bed CTV (orange contours, left panel) and inside the nodal CTV (green contours, center and right panels).

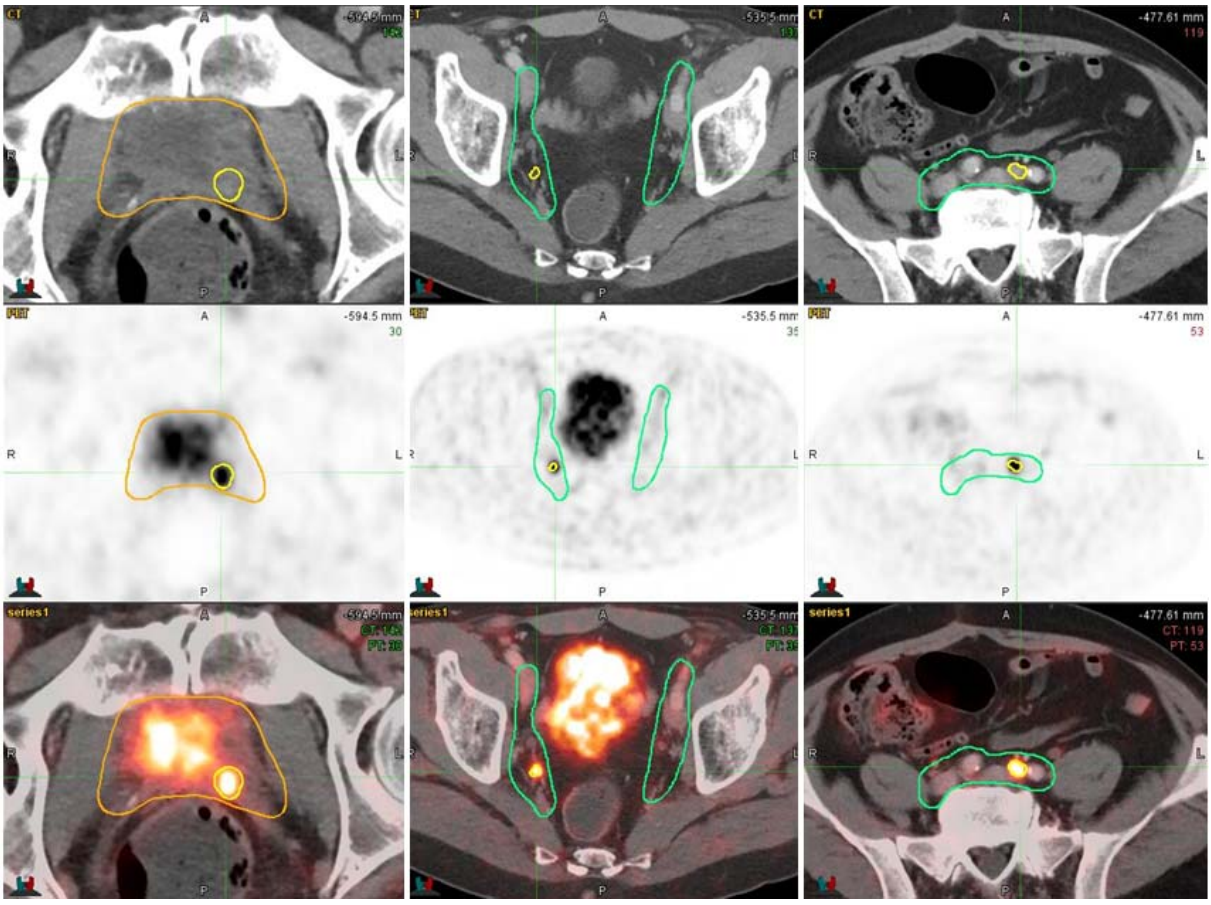
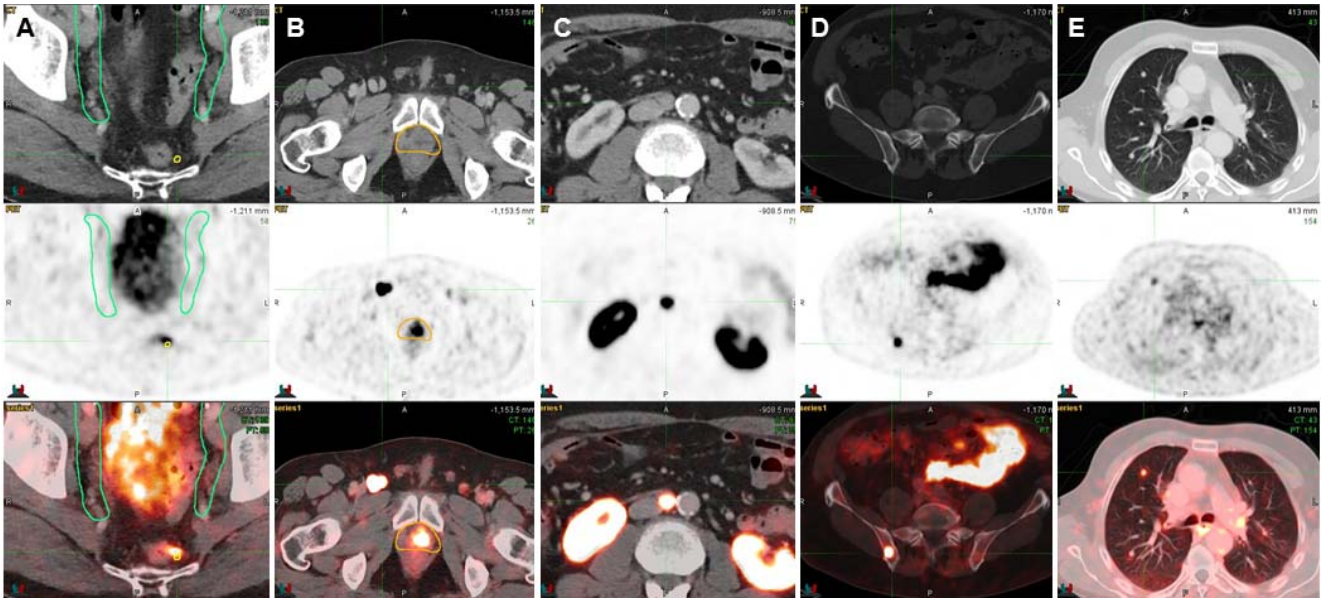


Figure 4: Examples of PSMA-positive lesions which are localized outside of consensus CTV from left to right: perirectal LN (A), inguinal LN (B), lumbo-aortic LN (C), bone (D), lung (E).



TABLES

Table 1: Clinical and pathologic characteristics of the 270 patients

Characteristics		*n* = 270
Age at PET/CT, median (years)		68 (range 43-90)
Initial PSA before Surgery, median (ng/ml)		8.3 (range 0.4-200)
	< 10	130 (48%)
	≥ 10 < 20	46 (17%)
	≥ 20	38 (14%)
	Unknown	56 (21%)
Gleason Score	≤ 6	33 (12%)
	7	135 (50%)
	≥ 8	86 (32%)
	Unknown	16 (6%)
Pathologic Primary Tumor Staging (pT)	pT2	99 (36.5%)
	pT3	142 (52.5%)
	pT4	2 (0.7%)
	Unknown	27 (10%)
Pathologic Regional LN Staging (pN)	pN0	166 (61.5%)
	pN1	54 (20%)
	pNx	50 (18.5%)
Positive Margin	R0	152 (56.5%)
	R1	67 (25%)
	Unknown	51 (19%)
NCCN Risk Group	Low	4 (1.5%)
	Intermediate	36 (13.5%)
	High	163 (60.5%)
	N1	54 (20%)
	Unknown	13 (5%)
ADT within 6 months prior to imaging		33 (12.5%)
Time between surgery and PET/CT, median (months)		25 (range 2-272)
Last PSA value prior to PET/CT, median (ng/ml)		0.44 (range 0.03-1)

Table 2: ^{68}Ga-PSMA-11 PET/CT patterns of relapse

Note that percentages do not add up to 100 as multiple disease localizations per patient were possible.

	Total Population *n* = 270 *number of patients (%)*
PSMA PET/CT +	132 (49%)
Prostate Bed (T+)	47 (17.5%)
Pelvic LN (N1)	83 (30.5%)
Extra-pelvic LN (M1a)	9 (3.5%)
Bone (M1b)	23 (8.5%)
Visceral (M1c)	3 (1%)
PSMA T+ N0 M0	32 (12%)
PSMA T0 N1 M0	59 (22%)
PSMA T+ N1 M0	8 (3%)
PSMA T+ N0 M1	2 (0.7%)
PSMA T0 N0 M1	15 (5.5%)
PSMA T0 N1 M1	11 (4%)
PSMA T+ N1 M1	5 (2%)

Table 3: Anatomic repartition of ^{68}Ga-PSMA-11 PET/CT positive findings and outside of planning volumes based on RTOG consensus CTV.

Note that percentages do not add up to 100 as multiple disease localizations per patient were possible.

	PSMA PET positive patients (n)	Outside of CTV patients (n)	PSMA PET positive lesions (n)	Outside of CTV lesions (n)	Median Size [mm] (range)	Median SUVmax (range)
Overall	132 (49%)	52 (19.5%)	304	119	6.0 (3.0-23.0)	5.7 (0.5-86.9)
Prostate Bed (T+)	47 (17.5%)	1 (0.003%)	52	1	7.0 (4.0-23.0)	6.4 (2.2-86.9)
Pelvic LN (N+)	83 (30.5%)	30 (11%)	174	39	6.0 (3.0-17.0)	5.8 (1.5-69.7)
Internal iliac	27 (10%)	2 (0.7%)	32	2	6.0 (3.0-10.0)	7.3 (2.3-55.0)
External Iliac	38 (14%)	9 (3.5%)	45	9	7.0 (3.5-15.0)	5.9 (1.5-69.7)
Obturator	19 (7%)	2 (0.7%)	24	2	6.0 (4.0-17.0)	3.5 (2.1-17.4)
Perirectal	18 (6.5%)	16 (6%)	25	19	5.0 (4.0-10.0)	5.2 (1.50-57.7)
Presacral	13 (5%)	3 (1%)	22	4	6.0 (4.0-10.0)	7.5 (1.5-45.7)
Common Iliac	16 (6%)	2 (0.7%)	26	3	6.0 (3.0-15.0)	5.9 (2.0-33.3)
Extra-pelvic LN (M1a)	9 (3.5%)	9 (3.5%)	28	28	8.0 (3.0-12.0)	13.6 (2.7-38.9)
Inguinal	2 (0.7%)	2 (0.7%)	7	7	-	-
Retro-peritoneal	6 (2%)	6 (2.2%)	15	15	-	-
Upper diaphragm	2 (0.7%)	2 (0.7%)	6	6	-	-
Bone (M1b)	23 (8.5%)	23 (8.5%)	39	39	-	5.3 (2.7-28.8)
Lung (M1c)	3 (1%)	3 (1%)	11	11	5.0 (4.0-7.0)	1.0 (0.5-2.6)

Table 4: Potential Impact of ^{68}Ga-PSMA-11 PET/CT imaging on salvage radiation therapy planning for early biochemical recurrence after primary prostatectomy.

	n = 270
Major impact on SRT planning - *Outside of RTOG CTV recurrence*	**52 (19%)**
Extension of the pelvic consensus CTV	19 (7%)
Superior extension to cover para-aortic LNs	5 (2%)
Oligometastasis-directed SBRT (≤5 M1a or M1b)	22 (9.5%)
RT futile due to polymetastatic or visceral disease (>5 M1a,M1b or M1c)	6 (2.5%)
Minor impact on SRT planning – *Covered by planning based on consensus CTV*	**80 (29.5%)**
Dose-escalation to gross disease *(^{68}Ga-PSMA-11 PET-positive disease)*	
No impact on SRT planning - *Negative ^{68}Ga-PSMA-11 PET/CT*	**138 (51%)**