

# <sup>68</sup>Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning

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Target volume delineations for prostate cancer (PCa) salvage radiotherapy (SRT) after radical prostatectomy are usually drawn in the absence of visibly recurrent disease. <sup>68</sup>Ga-labeled prostate-specific membrane antigen (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 affect target volume delineations for routine SRT. Our objective was to map the recurrence pattern of PCa early biochemical recurrence (BCR) after radical prostatectomy with <sup>68</sup>Ga-PSMA-11 PET/CT in patients with serum PSA levels of less than 1 ng/mL, determine how often consensus clinical target volumes (CTVs) based on the Radiation Therapy Oncology Group (RTOG) guidelines cover <sup>68</sup>Ga-PSMA-11 PET/CT-defined disease, and assess the potential impact of <sup>68</sup>Ga-PSMA-11 PET/CT on SRT. **Methods:** This was a post hoc analysis of an intention-to-treat population of 270 patients who underwent <sup>68</sup>Ga-PSMA-11 PET/CT at 4 institutions for BCR after prostatectomy without prior radiotherapy at a PSA level of less than 1 ng/mL. RTOG consensus CTVs that included both the prostate bed and the pelvic lymph nodes were contoured on the CT dataset of the PET/CT image by a radiation oncologist masked to the PET component. <sup>68</sup>Ga-PSMA-11 PET/CT images were analyzed by a nuclear medicine physician. <sup>68</sup>Ga-PSMA-11-positive lesions not covered by planning volumes based on the consensus CTVs were considered to have a potential major impact on treatment planning. **Results:** The median PSA level at the time of <sup>68</sup>Ga-PSMA-11 PET/CT was 0.48 ng/mL (range, 0.03–1 ng/mL). One hundred thirty-two of 270 patients (49%) had a positive <sup>68</sup>Ga-PSMA-11 PET/CT result. Fifty-two of 270 (19%) had at least one PSMA-11-positive lesion not covered by

the consensus CTVs. Thirty-three of 270 (12%) had extrapelvic PSMA-11-positive lesions, and 19 of 270 (7%) had PSMA-11-positive lesions within the pelvis but not covered by the consensus CTVs. The 2 most common <sup>68</sup>Ga-PSMA-11-positive lesion locations outside the consensus CTVs were bone (23/52, 44%) and perirectal lymph nodes (16/52, 31%). **Conclusion:** Post hoc analysis of <sup>68</sup>Ga-PSMA-11 PET/CT implied a major impact on SRT planning in 52 of 270 patients (19%) with PCa early BCR (PSA < 1.0 ng/mL). This finding justifies a randomized imaging trial of SRT with or without <sup>68</sup>Ga-PSMA-11 PET/CT investigating its potential benefit on clinical outcome.

**Key Words:** prostate cancer; PSMA; PET/CT; recurrence; salvage radiotherapy

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**P**rostate cancer (PCa) biochemical recurrence (BCR) takes place in 20%–80% of patients within 10 y after radical prostatectomy, with the risk of failure dependent on National Comprehensive Cancer Network risk group, pathologic features, and genomic classification (1,2). After BCR, salvage radiotherapy (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) level (5), radiotherapy dose (6), and risk group (7). For high-risk patients, 5-y BCR after SRT reaches 70% (8,9). Intuitively, SRT is curative only 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 of less than 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 Radiation Therapy Oncology Group (RTOG) published contouring guidelines for both prostate bed and pelvic lymph node (LN) clinical target

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volumes (CTVs) (areas with potential microscopic occult tumor) based on a consensus panel of experienced genitourinary radiation oncologists (11,12). These consensus CTVs are applied in ongoing clinical trials and guide routine care.

<sup>68</sup>Ga-labeled (Glu-NH-CO-NH-Lys-(Ahx)-[<sup>68</sup>Ga(HBED-CC)]) prostate-specific membrane antigen (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) and is also highly specific (16) and reproducible (17). Detection rates of about 50% are reported even at PSA levels of less than 0.5 ng/mL (15,16). Therefore, <sup>68</sup>Ga-PSMA-11 PET/CT has the potential to guide and improve target volume delineations for SRT.

The potential impact of <sup>68</sup>Ga-PSMA-11 PET/CT on radiotherapy planning has been assessed in several inhomogeneous patient groups with primary and recurrent disease. These studies established that <sup>68</sup>Ga-PSMA-11 PET/CT can image PCa at low serum PSA values and potentially affect 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 <sup>68</sup>Ga-PSMA-11 PET/CT at a PSA level of less than 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 map the <sup>68</sup>Ga-PSMA-11 PET/CT recurrence pattern of early BCR after prostatectomy, evaluate how often SRT based on consensus contouring guidelines fails to cover PSMA-11–expressing disease, and assess the potential impact of <sup>68</sup>Ga-PSMA-11 PET/CT on SRT planning for patients with PCa early BCR.

## MATERIALS AND 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 at Los Angeles [UCLA,  $n = 47$ ; clinicaltrials.gov identifier NCT02940262, Institutional Review Board approval 16-001095], Ludwig-Maximilians-University of Munich [ $n = 40$ ], and University of Essen [ $n = 36$ ]). All patients underwent radical prostatectomy, had BCR without prior radiotherapy, and underwent <sup>68</sup>Ga-PSMA-11 PET/CT at a serum PSA level of less than 1 ng/mL between August 2013 and May 2017 to detect the sites of recurrence. All patients gave written consent to undergo the procedures. The clinical data and DICOM files of all patients were anonymized and imported onto a dedicated radiotherapy contouring workstation at UCLA (MIM, version 6.7.5; MIM Software Inc.). The UCLA Institutional Review Board approved this anonymized post hoc retrospective analysis (approval #17-001340), and the requirement to obtain informed consent was waived.

### <sup>68</sup>Ga-PSMA-11 PET/CT Image Acquisition

<sup>68</sup>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 Healthcare Discovery 690 ( $n = 13$ , 5%). The <sup>68</sup>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 SRT Planning

SRT consensus CTVs were contoured on the CT dataset of the PET/CT scan for all 270 patients by an experienced radiation oncologist who was masked to the PET findings. Consensus RTOG contouring guidelines were used (Fig. 1A) (11,12), except that the common iliac nodes were contoured beginning inferior to L4/L5 (rather than L5/S1). Briefly, the prostate bed CTV included the anatomic 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 CTVs fails to cover PSMA-11–expressing recurrent disease.

### <sup>68</sup>Ga-PSMA-11 PET/CT Image Analysis

Next, all <sup>68</sup>Ga-PSMA-11 PET/CT images were analyzed by an experienced nuclear medicine physician according to recent recommendations (25,29): any focal uptake of <sup>68</sup>Ga-PSMA-11 above the surrounding background level and not associated with physiologic uptake or known pitfalls (30) was considered suggestive of malignancy (Fig. 1B). Distinction between malignant and inflammatory LNs (e.g., reactive or granuloma) was based on degree of PSMA-11 uptake, typically intermediate and low for inflammation, and location, typically perihilar, axillary, or inguinal for inflammatory nodes. On the basis of TNM staging, the following regions were systematically analyzed for recurrence: prostate bed/seminal vesicle remnants (T), pelvic LNs (N) (internal iliac, obturator, external iliac, perirectal, presacral, common iliac), extrapelvic LNs (M1a) (retroperitoneal, inguinal, chest, other), bone (M1b), and other visceral organs (M1c).

### <sup>68</sup>Ga-PSMA-11 PET Lesion Contouring

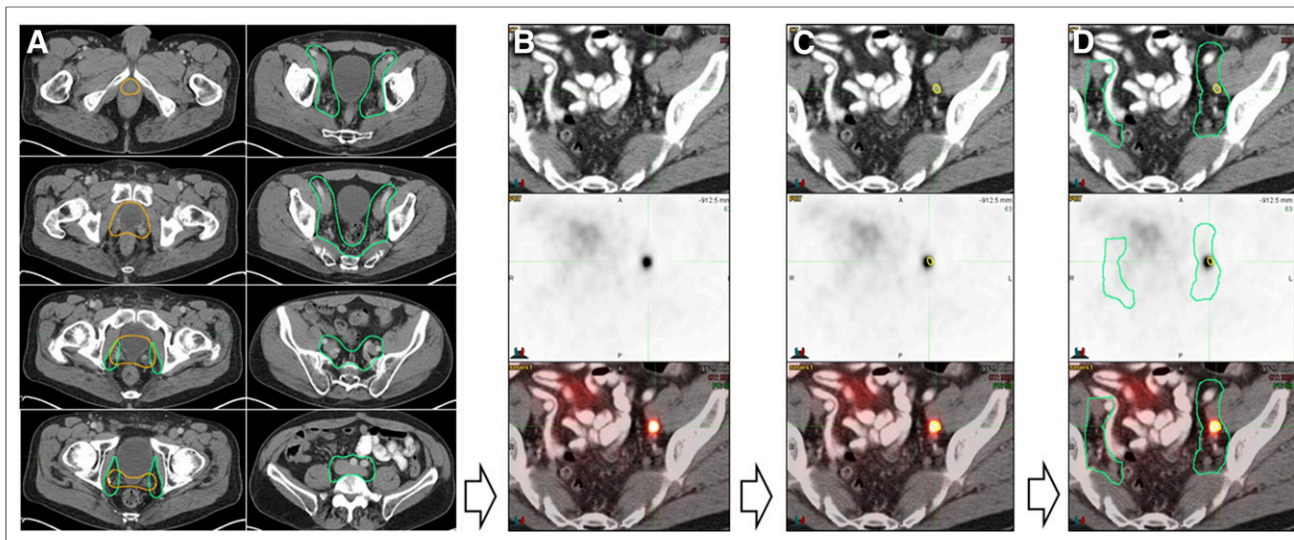
In a third step, <sup>68</sup>Ga-PSMA-11–positive lesions were contoured on the CT images (Fig. 1C). These contours were subsequently used to define <sup>68</sup>Ga-PSMA-11–based target volumes. Moreover, we generated a 3-dimensional map of all <sup>68</sup>Ga-PSMA-11–positive lesion contours across the entire study population on a template patient (Fig. 2). This was achieved by rigid image registration of each patient's CT image to the template patient image. Then, the <sup>68</sup>Ga-PSMA-11–based contours were transferred to the template patient image through this registration (MIM, version 6.7.5).

### Coregistration of Consensus CTVs with <sup>68</sup>Ga-PSMA-11 PET/CT Images

In a final step, the consensus CTVs were coregistered with the <sup>68</sup>Ga-PSMA-11 PET/CT images (Fig. 1D). Contours including the PSMA-11–positive lesions were then compared with the consensus CTVs for each patient to assess whether PSMA-11–positive lesions were localized inside (Fig. 3) or outside (Fig. 4) the consensus CTVs. To take into consideration the final planning target volumes, only PSMA-11–positive lesion contours at least 10 mm away from the CTVs were considered inadequately covered. Because many modern centers use CTVs to plan target volume expansions of less than 10 mm, this analysis should yield a generous estimate of how often planning based on consensus CTVs offers adequate coverage. PSMA-11–positive lesions within either the prostate bed or the pelvic LN consensus CTVs were considered covered.

### Potential Impact of <sup>68</sup>Ga-PSMA-11 PET/CT on Radiotherapy Planning

PSMA-11–positive lesions not covered by the consensus CTVs were considered to have a potential major impact on treatment planning. Potential major impact was further subclassified as extension of the CTVs to cover PSMA-11–positive lesions within the pelvis; superior extension of the CTVs to cover paraaortic LNs; addition of



**FIGURE 1.** Study methodology. (A) Experienced radiation oncologist masked to PET findings contoured RTOG CTVs onto CT dataset of PET/CT scan for all 270 patients (prostate bed CTV in orange and pelvic LN CTV in green). (B) All  $^{68}\text{Ga}$ -PSMA-11 PET/CT images were analyzed by an experienced nuclear medicine physician. (C) PSMA-11–positive lesions were contoured in yellow on CT images. (D) Consensus CTVs were coregistered with  $^{68}\text{Ga}$ -PSMA-11 PET/CT images and PSMA-11–positive lesion contours (yellow) to assess, for each patient, whether PSMA-11–positive lesions were localized inside or outside consensus CTVs.

metastasis-directed stereotactic body radiation therapy for extrapelvic oligometastatic disease (1–5 extrapelvic sites that are M1a or M1b); or radiotherapy not indicated (futile) because of the presence of visibly polymetastatic ( $>5$  M1a or M1b) or visceral (M1c) metastatic disease. If PSMA-positive lesions were covered by the CTVs, the potential impact of  $^{68}\text{Ga}$ -PSMA-11 PET/CT on treatment planning was defined as minor (potential for dose escalation to gross disease (visibly PSMA-11–positive). Negative  $^{68}\text{Ga}$ -PSMA-11 PET/CT findings 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  $^{68}\text{Ga}$ -PSMA-11 PET/CT

on SRT planning. Descriptive statistics were used (median, range). The comparisons of clinical and pathologic characteristics between positive and negative  $^{68}\text{Ga}$ -PSMA-11 PET/CT patients were conducted using the *t* test along with the Wilcoxon test as a verification for continuous variables and the  $\chi^2$  test for categorical variables. The serum PSA level before PET/CT was considered first as continuous variable and converted into categorical-variable—low PSA (0.5–1.0 ng/mL) and very low PSA ( $<0.5$  ng/mL)—groups for comparison. These analyses were conducted in R (31).

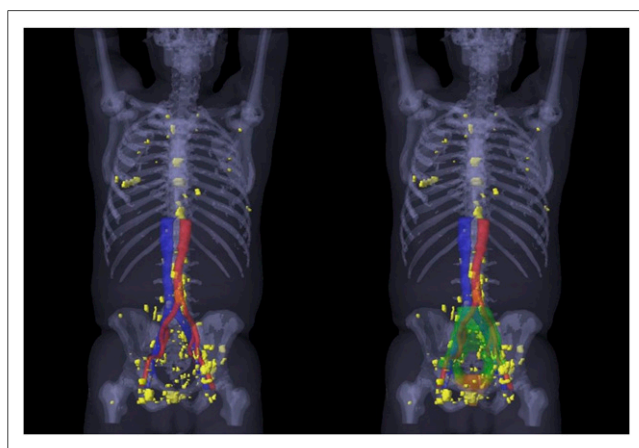
## RESULTS

### Patient Characteristics

Table 1 summarizes the clinical and pathologic characteristics of the 270 patients. In brief, the median age was 68 y (range, 43–90 y), and the median serum PSA level was 0.44 ng/mL (range, 0.03–1 ng/mL). Thirty-three of 270 patients (12.5%) underwent androgen deprivation therapy within 6 mo before the  $^{68}\text{Ga}$ -PSMA-11 PET/CT study. Thirty-six of 270 (13.5%) were National Comprehensive Cancer Network–defined intermediate-risk. One hundred sixty-three of 270 (60.5%) were National Comprehensive Cancer Network–defined high-risk, 142 of 270 (52.5%) were pT3, and 54 of 270 (20%) were pN1. Sixty-seven of 270 patients (25%) had positive surgical margins (R1). Overall, the cohort was at high risk for treatment failure after prostatectomy.

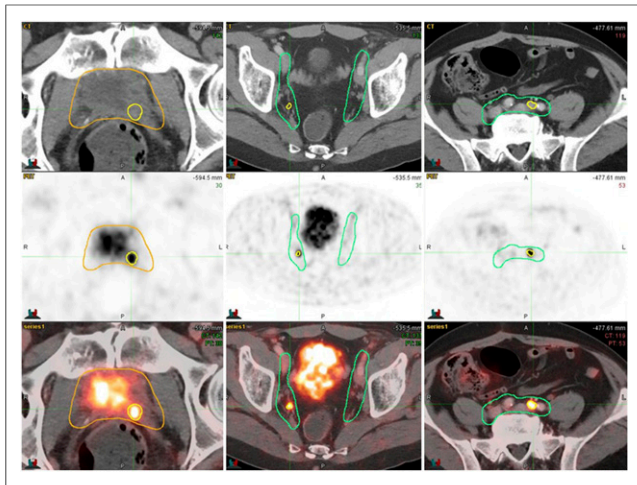
### $^{68}\text{Ga}$ -PSMA-11 PET/CT Findings and Consensus CTVs

Tables 2 and 3 depict the  $^{68}\text{Ga}$ -PSMA-11 PET/CT findings. One hundred thirty-two of 270 patients (49%) had a positive  $^{68}\text{Ga}$ -PSMA-11 PET/CT result. Fifty-two of 132 patients (39%) had at least one PSMA-11–positive lesion not covered by consensus CTVs: 33 of 132 (25%) had extrapelvic metastases whereas 19 of 132 (14%) had PSMA-11–positive pelvic lesions not covered by consensus CTVs, without extrapelvic metastases. The 3 most common  $^{68}\text{Ga}$ -PSMA-11–positive lesion locations outside the consensus CTVs were bone (23/52, 44%), perirectal LNs (16/52, 31%),



**FIGURE 2.** A 3-dimensional map of the PSMA-11–positive lesions (yellow) of all 52 patients with recurrence outside consensus CTVs (23 patients with recurrence outside only and 29 patients with recurrence outside and inside consensus CTVs), created by rigid registration of each patient's CT image to template patient's CT image, followed by transfer of each PSMA-11–positive lesion contour to template patient CT image (MIM, version 6.7.5; MIM Software Inc.). On right side, 3-dimensional prostate bed consensus CTV is shown in orange and 3-dimensional pelvic LN consensus CTV in green.





**FIGURE 3.** PSMA-11–positive lesions (yellow contours) inside prostate bed CTV (gold contours) and nodal CTV (green contours).

and distal external iliac LNs (9/52, 17%). Figure 2 displays a 3-dimensional map of all  $^{68}\text{Ga}$ -PSMA-11 PET recurrences outside the consensus CTVs coregistered on a template patient's CT image.

#### **$^{68}\text{Ga}$ -PSMA-11 PET/CT Findings and Clinicopathologic Characteristics**

The 132 positive  $^{68}\text{Ga}$ -PSMA-11 PET/CT patients had significantly higher PSA levels (median, 0.5 vs. 0.36 ng/mL;  $P < 0.001$ ) and shorter times to recurrence (median, 21.3 vs. 30.4 mo;  $P = 0.05$ ) than the 138 negative ones. The detection rate (at least one PSMA-11–positive finding) was significantly higher in patients with a Gleason score of more than 7 than in those with a Gleason score of 7 or less (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 less than 0.5 ng/mL (very low PSA group), and 117 had levels of 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-11–positive lesions not covered by the consensus CTVs had a borderline-significant dissimilar pattern in the low and the very low PSA groups (29/117 [25%] vs. 23/153 [15%];  $P = 0.06$ ).

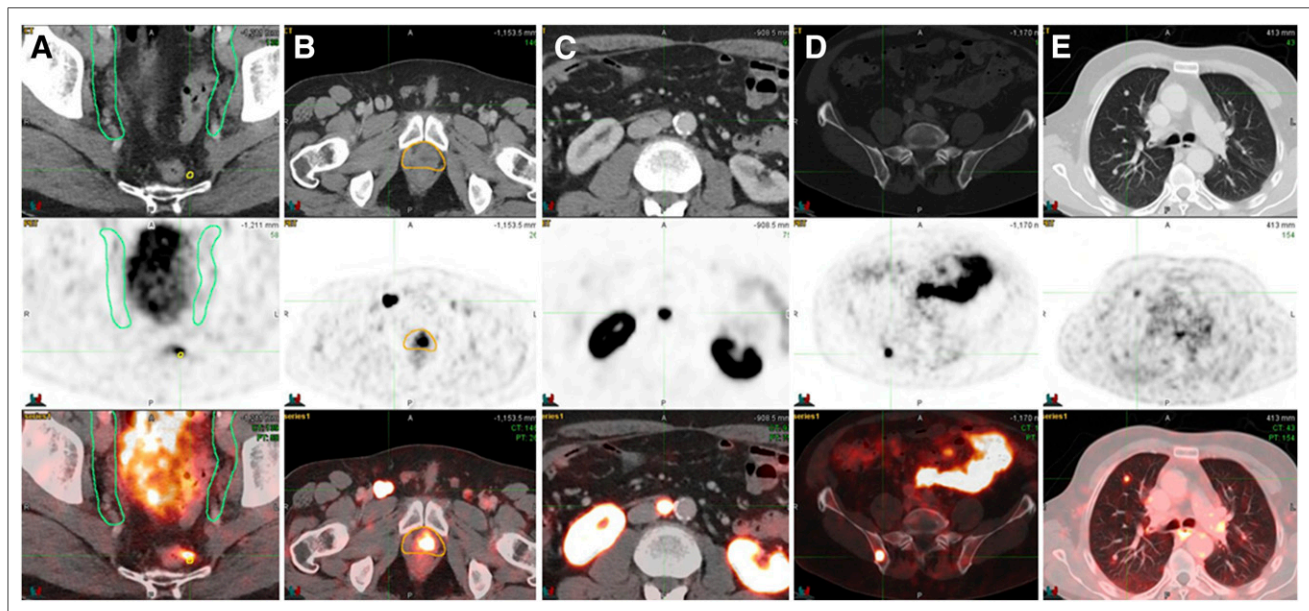
#### **Verification of PSMA-11–Positive Lesions Outside Consensus CTVs**

Lesions not covered by the consensus CTVs were verified in 24 of 52 patients (46%). This was done by biopsy ( $n = 1$ ), surgery ( $n = 3$ ), bone scanning ( $n = 1$ ), MRI ( $n = 1$ ), follow-up imaging (CT or PET/CT) showing progression at the site ( $n = 8$ ), follow-up imaging (CT or PET/CT) showing a response to treatment ( $n = 5$ ), or a decrease in serum PSA after focal treatment (stereotactic body radiation therapy;  $n = 5$ ).

#### **Potential Impact of $^{68}\text{Ga}$ -PSMA-11 PET/CT on SRT Planning**

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

**Potential Major Impact.** Fifty-two patients had at least one PSMA-11–positive lesion not covered by the consensus CTVs (19% of all 270 patients, 39% of 132 PSMA-11–positive patients). SRT based on consensus CTVs would not be curative for these patients. Nineteen patients with pelvic LN metastasis outside the consensus CTVs (7% of all 270 patients, 14% of 132 PSMA-11–positive patients) could have experienced extension of consensus CTVs to cover PSMA-11–expressing disease. Twenty-two of the 33 patients with extrapelvic metastases (67%) were oligometastatic ( $\leq 5$  metastatic sites), potentially eligible for metastasis-directed stereotactic body radiation therapy; 5 of 33 (15%) could



**FIGURE 4.** Examples of PSMA-11–positive lesions outside consensus CTVs: perirectal LN (A), inguinal LN (B), lumboaortic LN (C), bone (D), and lung (E).

**TABLE 1**

Clinical and Pathologic Characteristics of the 270 Patients

Characteristic	Data
Age at PET/CT, median (y)	68 (range, 43–90)
Initial PSA level 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 stage	
pT2	99 (36.5%)
pT3	142 (52.5%)
pT4	2 (0.7%)
Unknown	27 (10%)
Pathologic regional LN stage	
pN0	166 (61.5%)
pN1	54 (20%)
pNx	50 (18.5%)
Positive margin	
R0	152 (56.5%)
R1	67 (25%)
Unknown	51 (19%)
National Comprehensive Cancer Network risk group	
Low	4 (1.5%)
Intermediate	36 (13.5%)
High	163 (60.5%)
N1	54 (20%)
Unknown	13 (5%)
Androgen deprivation therapy within 6 mo before imaging	33 (12.5%)
Time between surgery and PET/CT, median (mo)	25 (range, 2–272)
Last PSA value before PET/CT, median (ng/mL)	0.44 (range, 0.03–1)

have experienced superior extension of the nodal CTVs to encompass the paraaortic LNs, and 6 of 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-11–positive patients) had PSMA-11–positive lesions covered by the consensus CTVs 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 <sup>68</sup>Ga-PSMA-11 PET/CT would have had a major impact on 19% of patients imaged (39% of PSMA-11–positive patients) and a minor impact on 30% (61%). Overall, the addition of <sup>68</sup>Ga-PSMA-11 PET/CT may affect SRT planning in half the patients with a PSA level of less than 1 ng/mL. Prospective clinical trials are necessary to assess the clinical value of a restaging <sup>68</sup>Ga-PSMA-11 PET/CT study before SRT.

Somewhat encouragingly, although most patients are at high-risk, treatment volumes based on consensus CTVs covered all PSMA-11–positive lesions for 61% of patients with a positive <sup>68</sup>Ga-PSMA-11 PET/CT result. This frequency is consistent with the historical success rate of SRT. However, consensus CTVs were inadequate to cover all PSMA-11–positive lesions in 39% of patients with a positive <sup>68</sup>Ga-PSMA-11 PET/CT result.

The detection rate of 49% for PSMA-11–positive lesions in this cohort with BCR after surgery and a low PSA level (<1.0 ng/mL) is consistent with previous reports (15,16). The anatomic distribution of PSMA-11–positive lesions is consistent with previous PET studies using choline and PSMA-11 ligands in the setting of BCR (9,19,24,32–35). The most common nodal regions outside the CTVs in patients in this study were the perirectal (*n* = 16), distal external iliac (*n* = 9), and paraaortic (*n* = 5), which are neither assessed by routine LN dissections at prostatectomy nor targeted by routine SRT. It is unlikely that a uniform expansion of the consensus CTVs to cover these regions would be feasible, given the risks of additional toxicity. Notably, most PSMA-11–positive

**TABLE 2**

<sup>68</sup>Ga-PSMA-11 PET/CT Patterns of Relapse

Pattern	Number of patients
PSMA-11 PET/CT+	132 (49%)
Prostate bed (T+)	47 (17.5%)
Pelvic LN (N1)	83 (30.5%)
Extrapelvic LN (M1a)	9 (3.5%)
Bone (M1b)	23 (8.5%)
Visceral (M1c)	3 (1%)
PSMA-11 T+ N0 M0	32 (12%)
PSMA-11 T0 N1 M0	59 (22%)
PSMA-11 T+ N1 M0	8 (3%)
PSMA-11 T+ N0 M1	2 (0.7%)
PSMA-11 T0 N0 M1	15 (5.5%)
PSMA-11 T0 N1 M1	11 (4%)
PSMA-11 T+ N1 M1	5 (2%)

Total population = 270. Percentages do not add up to 100 because multiple disease localizations per patient were possible.

**TABLE 3**

Anatomic Repartition of <sup>68</sup>Ga-PSMA-11–Positive Findings and Outside Planning Volumes Based on RTOG Consensus CTVs

Site	PSMA-11–positive patients (n)	Outside CTV patients (n)	PSMA-11–positive lesions (n)	Outside CTV lesions (n)	Median size (mm)*	Median SUV <sub>max</sub> *
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)
Extrapelvic 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	—	—
Retroperitoneal	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)

\*Data in parentheses are range.

Percentages do not add up to 100 because multiple disease localizations per patient were possible.

nodes were subcentimeter (median LN short axis: 6 mm [range, 3–17 mm]). Most PSMA-11–positive lesions in the prostate bed were covered. Furthermore, 32 patients (24% of the 132 PSMA-11–positive patients) had PSMA-positive lesions isolated to the prostate bed alone, whereas 67 of 132 patients (51%) had PSMA-11–positive lesions within the pelvis but without distant metastasis. This underscores the potential benefit of including pelvic nodal CTVs, which is currently under investigation in prospective trials (RTOG 0534, NCT00567580).

Importantly, the most common PSMA-11–positive lesion location outside the consensus CTVs was bone (23/52, 44%). No expansion of current CTVs would successfully cover these recurrences. Most M1 patients (67%) in this study were oligometastatic M1a or M1b (1–5 extrapelvic 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 stereotactic body radiation therapy) 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. <sup>68</sup>Ga-PSMA-11 PET/CT is probably the most sensitive imaging modality for selecting 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) and has ranged from 13.5% to 81.3%, with a median of 32%. Taken together, these studies found that the addition of choline PET/CT to SRT planning changed the initial plan in 357 of 1,083 patients (33%). However, <sup>68</sup>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

**TABLE 4**

Potential Impact of <sup>68</sup>Ga-PSMA-11 PET/CT Imaging on SRT Planning for Early BCR After Primary Prostatectomy

Impact	Data
Major impact on SRT planning—outside RTOG CTV recurrence	52 (19%)
Extension of pelvic consensus CTVs	19 (7%)
Superior extension to cover paraaortic LNs	5 (2%)
Oligometastasis-directed stereotactic body radiation therapy (≤5 M1a or M1b)	22 (9.5%)
Radiotherapy futile because of polymetastatic or visceral disease (>5 M1a, M1b, or M1c)	6 (2.5%)
Minor impact on SRT planning—covered by planning based on consensus CTVs; dose escalation to gross disease ( <sup>68</sup> Ga-PSMA-11–positive disease)	80 (29.5%)
No impact on SRT planning—negative <sup>68</sup> Ga-PSMA-11 PET/CT results	138 (51%)

Total population = 270.

lesion detection at low PSA values (<2 ng/mL). Therefore, a higher impact of <sup>68</sup>Ga-PSMA-11 PET/CT on SRT planning would be expected. Several prior studies did report on the potential impact of <sup>68</sup>Ga-PSMA-11 PET/CT imaging on radiotherapy planning (18–22,24,35). The impact ranged from 34% to 87%, with a median of 57%. However, these studies had limitations such as inhomogeneous patient groups, with primary and recurrent disease, and a wide range of serum PSA values and clinical disease states (18–24). Therefore, strengths unique to our study include the large number of patients (270), the fact that all patients had BCR after radical prostatectomy without prior radiotherapy, and the fact that all patients had a PSA level of less than 1 ng/mL at the time of <sup>68</sup>Ga-PSMA-11 PET/CT imaging. This is the most relevant patient cohort to assess the impact of <sup>68</sup>Ga-PSMA-11 PET/CT on SRT.

This was a post hoc retrospective analysis of a well-controlled patient cohort. The design of this study precludes analysis of the impact of <sup>68</sup>Ga-PSMA-11 PET/CT on clinical outcomes. To minimize bias, consensus CTVs were drawn with masking of the <sup>68</sup>Ga-PSMA-11 PET images. Another limitation was 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) after radical prostatectomy implied a major impact (19%) of <sup>68</sup>Ga-PSMA-11 PET/CT on SRT. This finding justifies a randomized prospective trial to determine whether <sup>68</sup>Ga-PSMA-11 PET/CT can improve outcomes in patients with PCa early BCR after radical prostatectomy.

## DISCLOSURE

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