Journal of Nuclear Medicine, published on February 9, 2023 as doi:10.2967/jnumed.122.265025

PSMA PET/CT–based Atlas for Prostatic Bed Recurrence after Radical Prostatectomy: Clinical Implications for Salvage Radiation Therapy Contouring Guidelines

Ida Sonni[1,2,3*], Alan Dal Pra[4*], Dylan P. O'Connell[5], Zachary Ells[1], Matthias Benz[1,2], Kathleen Nguyen[1], Stephanie M. Yoon[5], Jie Deng[5], Clayton Smith[5], Tristan Grogan[6], Nickolas G. Nickols[5,7], Minsong Cao[5], Amar U. Kishan[5**] and Jeremie Calais[1**]

1. Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
2. Department of Radiology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
3. Department of Experimental and Clinical Medicine, Nuclear Medicine Unit, Magna Graecia University, Catanzaro, Italy
4. Department of Radiation Oncology, University of Miami Miller School of Medicine, Miami, Florida, USA
5. Department of Radiation Oncology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
6. Department of Medicine Statistics Core, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
7. Department of Radiation Oncology, Veteran Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA.

Correspondence to: Ida Sonni, MD; Department of Radiological Sciences, David Geffen School of Medicine; University of California, Los Angeles, Los Angeles, CA, USA 90095-7370

E-mail: isonni@mednet.ucla.edu; **ORCID ID**: 0000-0002-8802-7704

* Co-first authors

** Co-senior authors

Keywords: PSMA PET, RTOG, prostate cancer, prostate bed recurrence, salvage radiation.

Total Words count: 5047

Running title: PSMA PET for prostate bed recurrence SRT

ABSTRACT

Purpose

The aim of this study was to analyze the patterns of prostate bed (PB) recurrence in prostate cancer patients experiencing PSA persistence (BCP) or biochemical recurrence (BCR) after radical prostatectomy using ^{68}Ga-PSMA-11 PET/CT (PSMA PET) in relation to the RTOG clinical target volumes (CTVs).

Methods

This single-center, retrospective analysis included patients with BCP or BCR post radical prostatectomy and PB recurrence on PSMA PET. Two nuclear medicine physicians and 4 radiation oncologists manually delineated the PB recurrence and the CTV using the RTOG contouring guidelines on the PSMA PET/CT, respectively, blinded from each other. The coverage of the PSMA PET recurrence was categorized as: PSMA recurrence completely covered, partially covered, or not covered by the RTOG-based CTV. Further, we evaluated the differences in PSMA recurrence patterns among patients with different PSMA PET staging (miTNM). Mann-Whitney U-tests, Chi-squared test, and Spearman ρ correlation analysis were used to investigate associations between CTV coverage and PSMA PET-based tumor volume, serum PSA levels, miTNM, and rectal/bladder involvement.

Results

226 patients were included in the analysis. 127 patients had PSMA recurrence limited to the PB (miTrN0M0), 30 had pelvic nodal disease (miTrN1M0), 32 had extra-pelvic disease (miTrN0M1), and 37 had both pelvic nodal and extra-pelvic disease (miTrN1M1). In the miTrN0M0 cohort, the recurrence involved the rectal and bladder wall in 12/127 (9%) and 4/127 (3%), respectively. The PSMA-positive PB recurrences were completely covered by the CTV in

68/127 (53%) patients, partially covered in 43/127 (34%), and not covered in 16/127 (13%). Full coverage was associated with smaller tumor volume (p=0.043), lack of rectal/bladder wall involvement (p=0.03) and lower miTNM staging (p=0.035), but not to lower serum PSA levels (p=0.979).

Conclusions

Our study suggests that PSMA PET can be a valuable tool for guiding SRT planning directed to the prostate bed in the setting of postoperative BCR or BCP. These data should be incorporated in the redefinition of PB contouring guidelines.

INTRODUCTION

Approximately one third of patients undergoing radical prostatectomy for prostate cancer will experience disease progression within 10 years (*1*-*3*). Postoperative radiotherapy to the prostate bed (PB) is a potential curative treatment option either in the presence of high-risk factors for local recurrence (adjuvant radiotherapy) or in patients with biochemical and clinical evidence of local recurrence (*4*).

The definition of the clinical target volume (CTV) for PB radiation has been guided by contouring guidelines mostly based on expert consensus rather than strict anatomical patterns of local recurrence (*5*-*8*). In the past decade, positron emission tomography targeting the prostate specific membrane antigen (PSMA PET) has emerged as an accurate and specific imaging tool for the evaluation of patients experiencing biochemical recurrence (BCR) of prostate cancer (*9*). Particularly after the FDA approval of the first PSMA-targeting PET radiopharmaceutical in December 2020 (*10*), PSMA PET has been increasingly implemented in this clinical setting (*11*) and can serve as an anatomic guide for salvage treatments. Therefore, new imaging modalities like PSMA PET could provide important information for a redefinition of the salvage radiotherapy contouring guidelines.

Herein we present a detailed analysis of local recurrences detected by ^{68}Ga-PSMA-11 PET/CT (PSMA PET) in men with prostate cancer experiencing PSA persistence (BCP) or biochemical recurrence (BCR) after radical prostatectomy. In addition, we assessed the location of these lesions in relation to the CTV recommendations by the RTOG contouring guidelines (*5*).

METHODS

Patients

We retrospectively screened all ^{68}Ga-PSMA-11 PET/CT scans acquired in our nuclear medicine clinic at UCLA between November 2016 and November 2020 as part of two prospective clinical studies enrolling patients with BCR or BCP (hereafter indicated as BCR) of prostate cancer post-radical prostatectomy (NCT02940262, NCT03582774). Men with prostate cancer treated with radical prostatectomy undergoing PSMA PET for BCR were included in our analysis if their clinical report described a recurrence in the PB. BCR was defined as a PSA of 0.2 ng/mL or more measured more than 6 weeks after prostatectomy (*9*). The flowchart in Figure 1 shows the patient selection process. Patients' clinical history and clinical data were collected from electronic medical records. This retrospective analysis was approved by the Ethics Committee (UCLA IRB#20-001948), which waived the necessity for study specific consent.

PSMA PET/CT

The PSMA-targeting ligand used for the PSMA PET was ^{68}Ga-PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)]) (*12*). Images were acquired using a 64-detector PET/CT scanner (2007 Biograph 64 Truepoint or 2010 Biograph mCT 64; Siemens, Munich, Germany). A diagnostic CT scan (200–240 mAs, 120 kV) was obtained after intravenous or oral contrast administration, unless contraindicated. A whole-body scan was acquired from pelvis to vertex prior to a dedicated post-void pelvic scan. The latter was not used for the analysis. All PET images were reconstructed with corrections for attenuation, dead-time, random events, and scatter, using iterative ordered-subsets expectation. The time per bed position was based on patient weight (*13*).

PSMA PET analysis and prostate bed recurrence contouring

The clinical PSMA PET reports were used to screen patients who had a suspected PB recurrence after RP. The description of the miTNM staging on the clinical reports was confirmed by one investigator (MB) who retrospectively reviewed all PSMA PET scans. After confirming the presence of a PB recurrence on the PSMA PET, two board certified nuclear medicine physicians (IS, MB) manually delineated the PB lesions according to the ^{68}Ga-PSMA PET procedure guidelines (*14*) using the 2D and 3D brush tools on MIM v 7.7.5 (MIM Software Inc., Cleveland, OH). A third nuclear medicine physician (JCa) was involved in cases deemed difficult and a consensus was achieved between the three readers. PSMA PET-based lesion volumes were recorded.

PSMA PET scans were visualized using a default upper SUVmax threshold of 5. Due to the variable intensity of PSMA uptake by different lesions and interference of physiologic urinary bladder uptake, often obscuring visualization of recurrences in its proximity, readers used manual adjustments of the SUVmax window thresholds based on each individual case, to help distinguish physiologic from pathologic uptake (*14*). Whenever possible and deemed useful by the readers, the fused CT images were used to facilitate lesion delineation.

The CT component of the PSMA PET/CT was used to assess the relation between the PSMA-based recurrence and significant anatomical structures (i.e. the rectal and bladder wall). Any PSMA-avid lesions overlapping the rectal or bladder wall on CT was described as involving the rectal or bladder wall. The association between rectal or bladder wall involvement and the PSMA recurrences was assessed. The PSMA PET readers described each patient's disease spread using the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria and the molecular imaging TNM (miTNM) (*15*). Briefly, the presence of a PB recurrence

was described as Tr, pelvic lymph node involvement as N1, extra-pelvic nodal and/or distant organs involvement as M1, pelvic nodal and extra-pelvic disease as N1 M1. The miTNM was used for a sub-analysis investigating the correlation between the CTV coverage and the PSMA PET-based disease stage.

RTOG-based CTV contouring

The CTV contours were delineated on the CT component of each PSMA PET/CT by 4 radiation oncologists (JD, SMY, CS, AUK) blinded to the PSMA component of the imaging scan, and to the lesions contoured on the PSMA PET. The delineation of the prostate bed CTV followed the recommendations of the RTOG contouring guidelines (*5*). In summary, the inferior border of the CTV extended inferiorly 8-12 mm from the vesicourethral anastomosis (VUA), and the superior border from the level of the caudal vas deferens remnant. The anterior border of the CTV extended to the posterior border of the pubis up to the top of the pubic symphysis, and the posterior border to the anterior rectal wall. Laterally, at the caudal level, the CTV extended to the levator ani muscle. Above the pubic symphysis, 1-2 cm of the bladder wall was included in the CTV; posteriorly, the CTV extended to the mesorectal fascia, and laterally, to the sacro-recto-genitopubic fascia.

Coverage analysis and heat map

Two of the investigators, a nuclear medicine physician (IS) and a radiation oncologist (ADP), assessed the CTV coverage of the PB PSMA PET-based recurrence in consensus using three pre-specified outcomes as follows: PSMA PET recurrence completely covered, partially covered, or not covered by the CTV. The three outcomes were further combined into: PSMA PET recurrence

completely covered by CTV and not completely covered by CTV (including the partially covered and not covered by the CTV outcomes). In case the PSMA PET recurrence was not completely covered by the CTV, the border of PB exceeded by the PSMA PET recurrence was described as anterior, posterior, lateral, inferior, superior, and combinations of them. Individual examples of the image analysis findings are shown in Figure 2.

A two-dimensional (2D) heat map showing the PB recurrence distribution patterns was created (DPOC, MC) by mapping all PSMA PET contours onto a template patient's CT through manual rigid registration for the whole cohort and for each miTNM staging (Figure 3). A 3D representation of all recurrences was generated (ZE) by using 3D Slicer (http://www.slicer.org)(*16*).

As a secondary objective, we conducted a sub-analysis evaluating the differences in PSMA PET recurrence patterns among patients with different miTNM staging (i.e. miTrN0M0, miTrN1M0, miTrN0M1 and miTrN1M1).

Statistical analysis

To assess the association between dichotomized CTV coverage status (fully vs not fully covered – including the partially covered and not covered outcome) and serum PSA levels we used the Mann-Whitney U-test due to the distributional properties of PSA levels. Similarly, we compared PSMA-based tumor volume and rectal/bladder involvement to dichotomized CTV coverage status. To investigate the association between the miTNM stage and the CTV coverage (e.g. fully, partially, and not covered) we used chi-squared test. Descriptive statistics are expressed as median (IQR), unless stated otherwise. All statistical analyses were conducted using Jamovi version 2.2.5 (The jamovi project (2021) retrieved from https://www.jamovi.org) and p-values <0.05 were considered statistically significant.

RESULTS

Patient population

A total of 2451 PSMA PET scans performed between November 2016 and November 2020 were screened for inclusion criteria. 226/2451 (9%) were included in this retrospective analysis. The median (IQR) time interval between radical prostatectomy and PSMA PET was 77 months (28 – 128). Table 1 shows the clinical characteristics of all patients and the different cohorts included in the sub-analysis. Of 226 patients, 127 (56%) had PB limited disease (miTr N0 M0), 30 (13%) were classified as miTr N1 M0, 32 (14%) as miTr N0 M1, and 37 (16%) as miTr N1 M1. The main cohort included 127 patients, while patients with spread of disease outside the PB were included in a separate a sub-analysis.

CTV coverage of PSMA PET recurrence

The PSMA PET PB recurrences were fully covered by the CTV in 68/127 (54%) patients, partially covered in 43/127 (34%) patients, and not covered in 16/127 (13%) patients. In the latter two groups, the PSMA PET recurrences extended beyond the CTV at the following locations: posteriorly (30/59, 51%), postero-laterally (14/59, 24%), postero-inferiorly (3/59, 5%), anteriorly (1/59, 2%), superiorly (1/59, 2%), and inferiorly (10/59, 17%) (Table 2, Figures 4 and 5).

Impact of serum PSA levels and tumor volume on CTV coverage

The median serum PSA level at time of PSMA PET in the miTr N0 M0 cohort was 1.02 ng/ml (IQR: 0.5 – 2.18; range: 0.10 – 57.6 ng/ml). In patients with PB recurrences fully covered, partially covered and fully outside the CTV, serum PSA levels were 1.11 ng/ml (0.5 – 2.2; range: 0.10 –

28), 1.09 ng/ml (0.46 – 2.63; range: 0.20 – 57.63) and 0.84 ng/ml (0.62 – 1.11; range: 0.23 – 7.8), respectively.

Thirty-four/127 (27%) patients had a serum PSA level ≤0.5 ng/ml, and 93/127 (73%) > 0.5 ng/ml. The CTV coverage outcome was not associated with serum PSA levels (p=0.98) nor with PSA levels ≤0.5 ng/ml (p=0.75). In the 34 patients with PSA levels ≤0.5 ng/ml the PSMA PET PB recurrences were fully covered by the CTV in 19/34 (56%) patients, partially covered in 12/34 (35%) patients, and not covered in 3/34 (9%) patients. In the latter two groups, the PSMA PET recurrences extended beyond the CTV at the following locations: posteriorly (8/15, 53%), postero-laterally (3/15, 27%), and inferiorly (4/15, 20%).

The median volume of PSMA PET recurrence was 0.72 ml (IQR: 0.04 - 15; range: 0.04 – 15). In patients with PB recurrences completely covered, partially covered and not covered by the CTV, tumor volumes were 0.57 ml (0.36 – 1.13; range: 0.08 – 11.09), 1.01 ml (0.49 - 67; range: 0.13 - 15) and 0.68 ml (0.37 – 0.96; range: 0.04 – 4.72), respectively. Complete CTV coverage was significantly associated to smaller tumor volume (p=0.04).

Impact of adverse pathology features after surgery on the CTV coverage

In patients with surgical margin involvement (31/127, 24%) the PSMA PET PB recurrences were fully covered by the CTV in 21/31 (68%) patients, partially covered in 9/31 (29%) patients, and not covered in 1/31 (3%) patients. In patients without surgical margins involvement (58/127, 46%) the PSMA PET PB recurrences were fully covered by the CTV in 26/58 (45%) patients, partially covered in 20/58 (34%) patients, and not covered in 12/58 (21%) patients. For 38/127 (30%) patients the information regarding surgical margin involvement was not available.

Impact of rectal/bladder wall involvement on the CTV coverage

PB lesions involved the rectal wall in 12/127 (9%) and bladder wall in 4/127 (3%) of patients. Rectal and/or bladder wall involvement was significantly associated with lack of full CTV coverage (p=0.03).

Impact of miTNM stage on the CTV coverage

Clinical characteristics, location of recurrences and CTV coverage patterns of the full cohort (miTr Nx Mx) are summarized in Table 1. In the miTr Nx Mx cohort the PSMA PET PB recurrence were completely covered by the CTV in 107/226 (46%) patients, partially covered in 91/226 (41%) patients, and not covered in 28/226 (13%) patients. In the latter two groups, the PSMA PET recurrences extended beyond the CTV at the following locations: posteriorly (57/119, 48%), postero-laterally (34/119, 29%), postero-inferiorly (8/119, 7%), anteriorly (1/119, 1%), antero-inferiorly (1/119, 1%), superiorly (4/119, 3%), laterally (2/119, 2%), and inferiorly (12/119, 10%) (Table 1 and Supplementary Table 1).

The percentage of PSMA PET recurrences completely covered by the CTV was 46%, 35% and 38% in the miTrN1M0, miTrN0M1, and miTrN1M1 sub-cohorts, respectively.

The PB recurrences involved the rectal and bladder wall were 19/226 (8%) and 10/226 (4%), respectively. Tumor involvement of the rectal and/or bladder wall was significantly associated with lack of complete CTV coverage in the full cohort (p=0.007).

The median serum PSA levels at time of imaging and PSMA PET-based tumor volume were 1.21 ng/ml (IQR: 2.40) and 0.88 ml (IQR: 1.24), respectively. Complete CTV coverage was significantly associated with smaller tumor volume (p=0.009), and not with lower serum PSA (p=0.76).

DISCUSSION

Our study showed that in a cohort of 127 patients with prostate cancer local recurrence limited to the PB (N0M0), the RTOG-based CTV fully or partially covered the PSMA PET prostate bed recurrences in 87% of the cases, while 13% of the recurrences were not covered by the CTV whatsoever. This work provides important information on patterns of PB recurrence based on novel imaging, indicating areas of potential failures that would not be covered by the current RTOG contouring guidelines for salvage prostate bed RT (SRT).

It is difficult to define standardized target volumes for radiation treatment after radical prostatectomy. The surgical removal of the prostate alters the anatomy of the pelvic organs, which causes significant challenges to radiation oncologists who contour SRT volumes due to significant patient heterogeneity. To date, the target delineation (CTV) for SRT to the PB is guided by consensus guidelines made by experts, but do not account for data from contemporary imaging, such as PSMA PET. Our study used ^{68}Ga-PSMA-11 PET/CT to generate a 3-D heat map of the PB recurrence patterns after radical prostatectomy in relation with the RTOG-based CTVs with the intent to guide the re-definition of these consensus contours.

While many groups investigated the patterns of failure after prostatectomy for PCa using PSMA PET, our work represents a large dataset that specifically focuses on the detailed description of patterns of local failure in the prostate bed using PSMA PET (*17*). In 47% of patients from our cohort, the RTOG-based CTVs did not cover completely the PB recurrences identified on PSMA PET (*18*). We observed that in the majority of cases without full coverage, recurrences extended beyond the CTV posteriorly, specifically at the posterior, postero-lateral and postero-inferior borders in 80% of cases, and in 17% of cases at the inferior border. The PSMA PET recurrences rarely overlapped the CTVs anteriorly (2%) or superiorly (2%), indicating an overall adequate

coverage on these areas. In fact, we believe that the current RTOG recommendations of extending the coverage anteriorly to the top of the pubic symphysis irradiates a large volume of normal bladder tissue unnecessarily given the low probability of recurrences in that area. Therefore, our work provides important information also for a potential reduction of the CTV antero-superiorly to potentially reduce toxicity rates. Further, they provide a potential explanation for why dose-escalation to the prostate fossa has failed to improve BCR outcomes in two randomized trials in the postoperative setting, while consistently improving BCR outcomes in multiple trials in the intact prostate setting (*19,20*). While it is true that these trials included patients with serum PSA lower than those of our cohort, a sub-analysis of our study specifically looking at CTV coverage in patients with serum PSA levels ≤0.5 ng/ml found that the proportions of PB recurrences fully covered and not fully covered were comparable to those of the full cohort. This finding further confirms that PSA levels are not significantly associated with the coverage outcome.

Overall, our results highlight the need for adequate contouring at the posterior border, although RTOG guidelines already recommend extending the posterior treatment volume to the anterior wall of the rectum. This finding can be partly explained by the possible posterior extension of the recurrences to involve the rectal wall, by possible inaccuracies due spill-over effect, as described above, and in part by the lack of strict adherence to the guidelines. In addition, a more extensive coverage at the postero-lateral angles on both sides of the rectum may be needed. It is important to mention that recurrences outside of the CTV could have been adequately covered by the planning target volumes (PTV) margin expansions. However, the PTV are intended to account for uncertainties in planning or treatment delivery rather than uncertainties in the true anatomical location of disease. A more definitive conclusion on the need for target volumes expansions would require validation on a cohort of patients with local failures after salvage radiotherapy.

Our findings are corroborated by a recent study from Australia (*21*) assessing patterns of failure in relation to the Faculty of Radiation Oncology Genito-Urinary Group (FROGG) and RTOG recommendations. These authors mapped the recurrences relative to vesicourethral anastomosis and showed that the RTOG CTV had a better coverage compared to FROGG. They similarly showed the importance of including the posterolateral rectal recesses, and possibly excluding the anterosuperior portion of the CTV.

The results of our sub-analysis investigating the patterns of PB recurrences regardless of the N and M status showed that the percentage of PSMA PET recurrences completely covered by the CTV was smaller in patients with wider spread of disease than in those with disease limited to the PB: 46%, 35%, and 38% in the miTr N1M0, miTr N0M1, and miTr N1M1 sub-cohorts, respectively. The locations of the PSMA PET contours exceeding the CTV were instead similar among the main cohort and the subcohorts, with the vast majority of them extending beyond the posterior, postero-lateral and postero-inferior borders (84%), with a smaller percentage at the inferior border (10%) and a minority at the anterior, superior and lateral borders (6%).

Our study further assessed the correlation of the CTV coverage of PB recurrences with clinical and imaging parameters. The involvement of the rectal and/or bladder wall, identified in 12/127 (9%) and 4/127 (3%) cases, respectively, was found to be significantly associated to worse coverage ($p= 0.03$). The urinary bladder and the rectum are anatomical landmarks used to delineate the prostate bed and represent crucial organs for the definition of the clinical target volumes used for SRT. Increased dose to normal tissues is associated to acute and late GI and GU side effects that significantly decrease patient's quality of life. In fact, radiotherapy quality assurance data from a recent prospective study have confirmed that an overlap of the CTV with rectal wall is associated with increased toxicity (*22*).

In our study, PSA and tumor volume were positively correlated with each other, but tumor volume was the only parameter associated with worse coverage. The PSMA-based tumor volumes were significantly associated with PSMA-based recurrence coverage (p=0.043), while serum PSA levels at time of PSMA PET were not (p=0.979).

An important aspect that needs to be taken into consideration when interpreting the results of our study is the intrinsic limitation of tumor contouring using PET due to its finite spatial resolution. Tumor delineation done on PSMA PET images inevitably suffers from partial volume and spillover effect, which can be described as part of the signal coming from the source (tumor) spilling out and being seen outside the location of the source (*23*). The ultimate result is an over-estimation of the actual tumor volumes, particularly significant for small lesions. In an attempt to overcome this limitation, the nuclear medicine readers used the fused CT images of the PSMA PET/CT as an aid for the delineation of the tumor, whenever possible. However, CT does not provide sufficient soft-tissue contrast and its utility is limited (*24*). This is valid also for the definition of rectal or bladder involvement, which is often not possible based on CT images. Therefore, interpretation of the analysis regarding rectal/bladder wall involvement should take into consideration this limitation. The use of information from MRI, and ideally the use of PET/MRI would have been the best approach to minimize this intrinsic limitation and obtain more accurate tumor extent delineation. Other limitations of our study are the lack of follow up information on our cohort and its retrospective nature. The authors are currently following up this cohort, and a study investigating the differences in progression free survival in these patients treated with SRT is planned (*25*).

Ideally, using a personalized approach with PSMA PET prior to SRT would allow us to weigh the potential benefits and harms of extending the RT coverage on an individual basis. A recent

study found that the use of SUVmax from PSMA PET could identify patients who are at higher risk for progression after SRT and might therefore benefit from a personalized treatment approach (*26*). However, in practice, when PSMA PET is not available, data from studies like ours should be used to redefine the prostate bed contouring guidelines with two main objectives: improve coverage of PB recurrences and decrease the unnecessary irradiation of healthy tissues much less likely to harbor prostate cancer recurrence.

CONCLUSIONS

Our study showed that in patients experiencing PSA persistence or BCR post-RP with disease limited to the PB on PSMA PET (miTrN0M0), the RTOG contouring guidelines for SRT cover the full extent of disease in 54% of the patients, leaving 34% partially treated and 13% untreated. Our study suggests that PSMA PET can be a valuable tool for SRT planning in the setting of BCR for patients with disease limited to the PB and should be incorporated into a redefinition of SRT contouring guidelines.

Disclosure statement

Alan Dal Pra reports research support to institution/sponsor – Veracyte, outside of the submitted work. Advisory board membership – Merck, outside of the submitted work.

Nicholas Nickols reports research support from Lantheus, Janssen, Bayer, outside the submitted work, and consulting for PrimeFour outside the submitted work.

Amar U. Kishan reports funding support from grant P50CA09213 from the Prostate Cancer National Institutes of Health Specialized Programs of Research Excellence, grant W81XWH-22-1-0044 from the Department of Defense, grant RSD1836 from the Radiological Society of North America, the STOP Cancer Organization, the Jonsson Comprehensive Cancer Center, and the Prostate Cancer Foundation; personal fees from Varian Medical Systems, Inc., ViewRay Inc., and Intelligent Automation, Inc.; and research support from ViewRay, Inc., the American Society for Radiation Oncology (ASTRO), the Prostate Cancer Foundation, and the Jonsson Comprehensive Cancer Center, all outside the submitted work.

Jeremie Calais reports prior consulting activities for Advanced Accelerator Applications, Astellas, Blue Earth Diagnostics, Curium Pharma, DS Pharma, EXINI, GE Healthcare, Isoray, IBA RadioPharma, Janssen Pharmaceuticals, Lightpointmedical, Lantheus, Monrol, Novartis, Progenics, POINT biopharma, Radiomedix, Sanofi, Telix Pharmaceuticals, outside of the submitted work.

No other potential conflicts of interest relevant to this article exist.

Figures and Tables

Figure 1. Flow chart of the screening process.

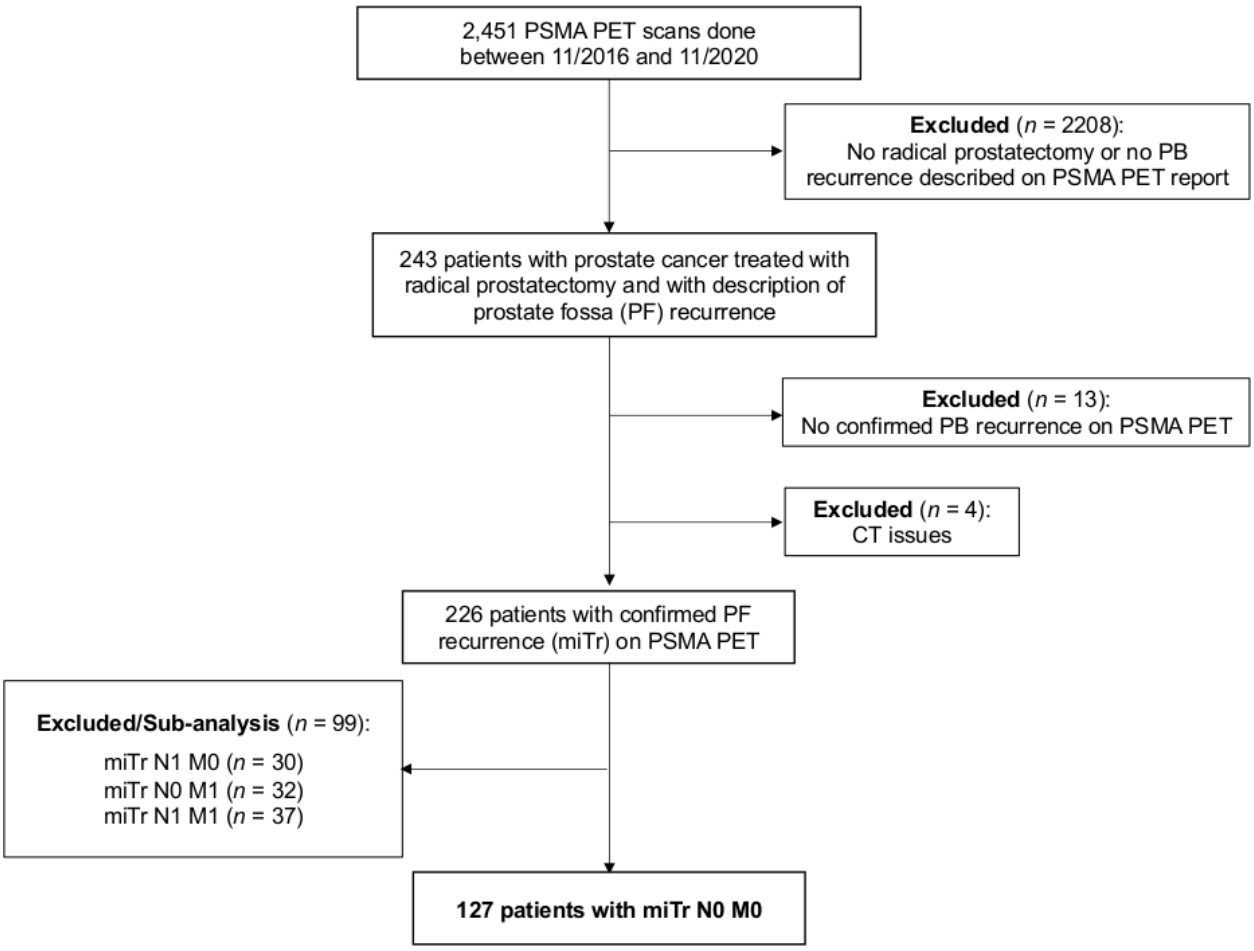


Figure 2. Definition of the location of PSMA PET lesion exceeding the CTV borders. PSMA PET contours are in light blue and CTV contours are in pink. PSMA PET lesion extending beyond the CTV at the posterior (A), inferior (B), lateral (C), superior (D), anterior (E), postero-inferior (F) and postero-lateral border (G).

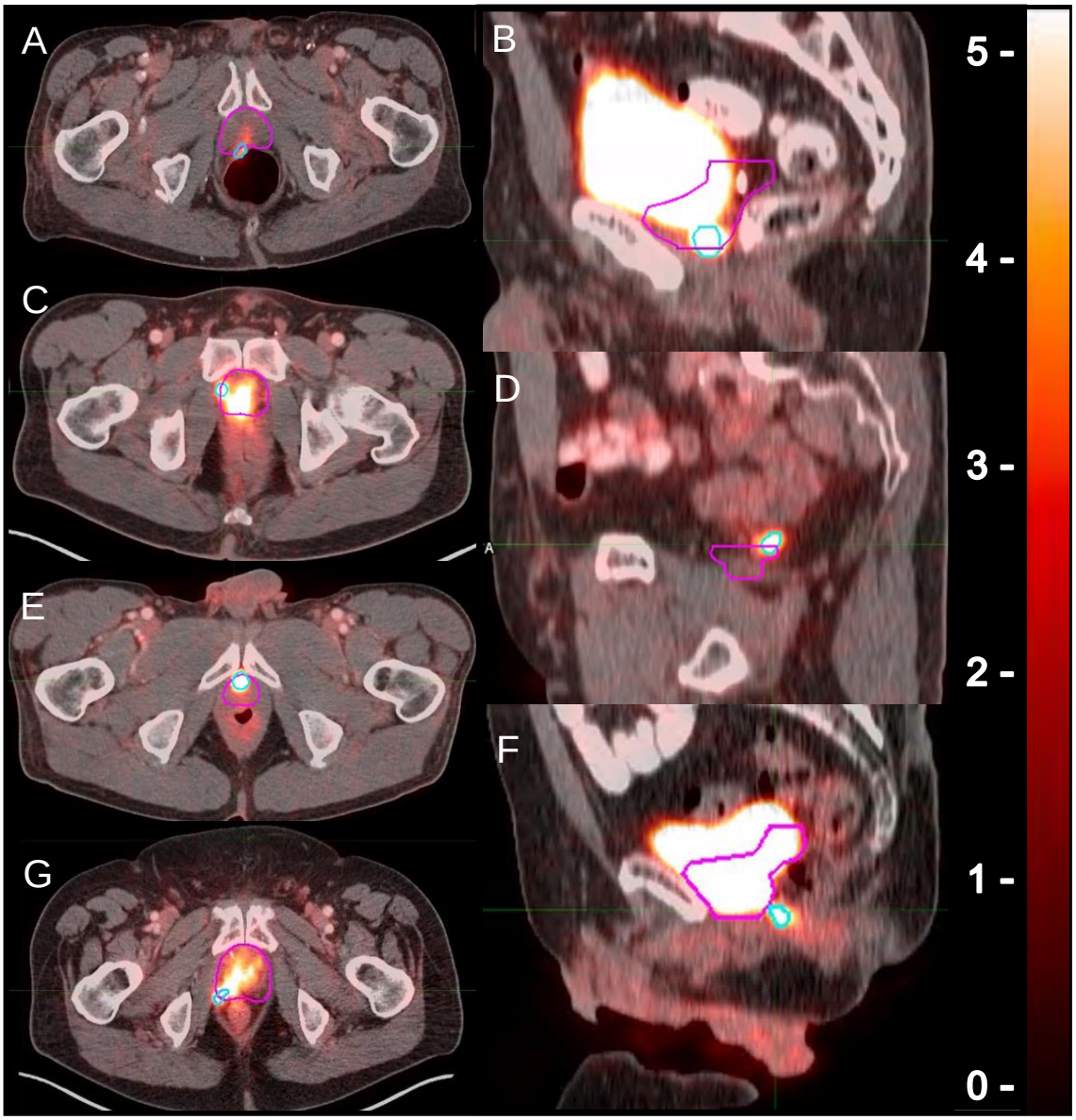


Figure 3. Heat map of prostate bed PSMA PET recurrences distribution in the miTr N0 Mo cohort (n=127 patients) mapped on a template patient's anatomy (the green contour represents the CTV).

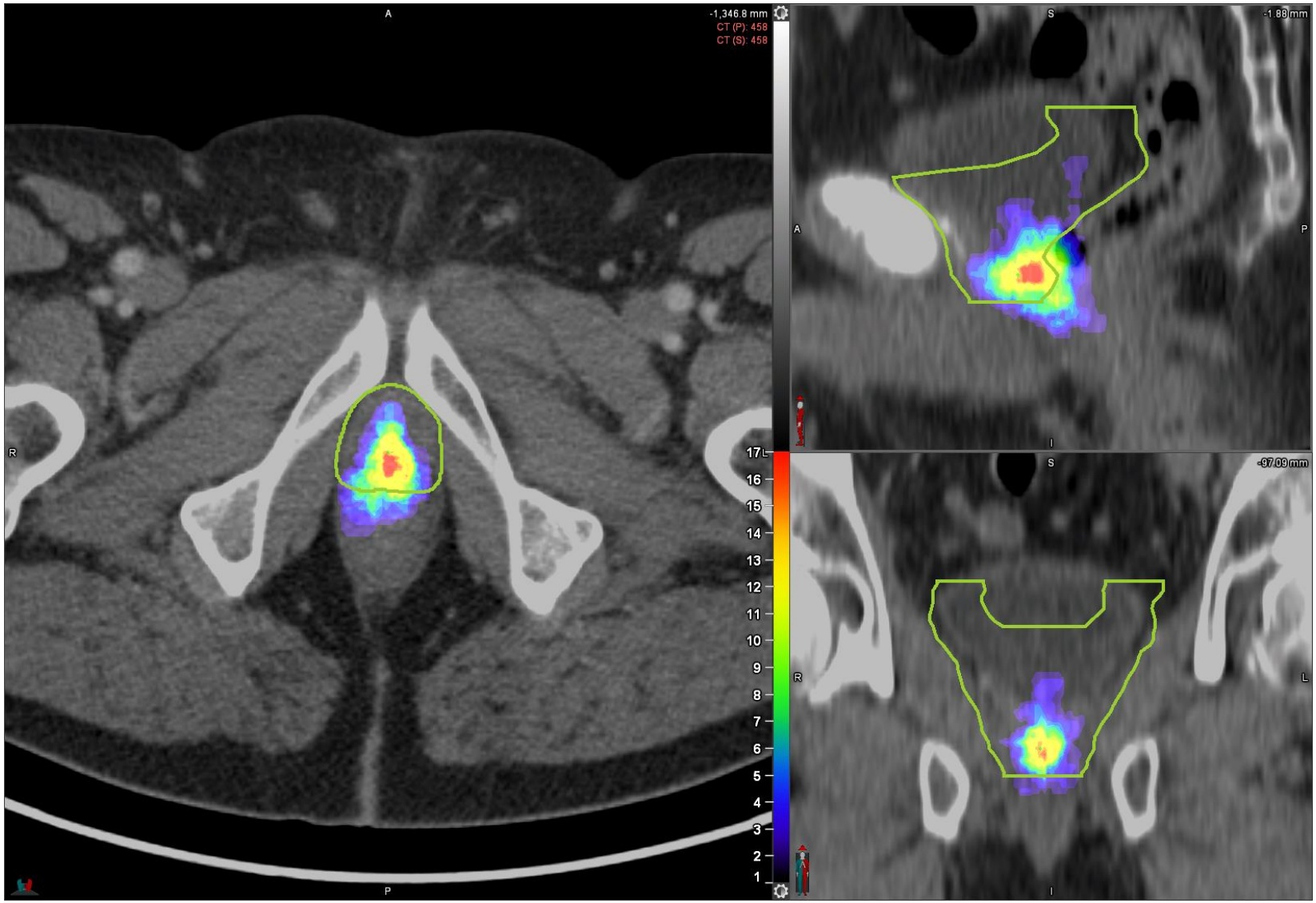


Figure 4. 3D rendering of all PB recurrence in relation to the RTOG-based CTV volume (light green), rectum (brown), and urinary bladder (pink) of a template patient. PSMA recurrences are in solid colors: completely covered in green, partially covered in yellow, not covered in red.

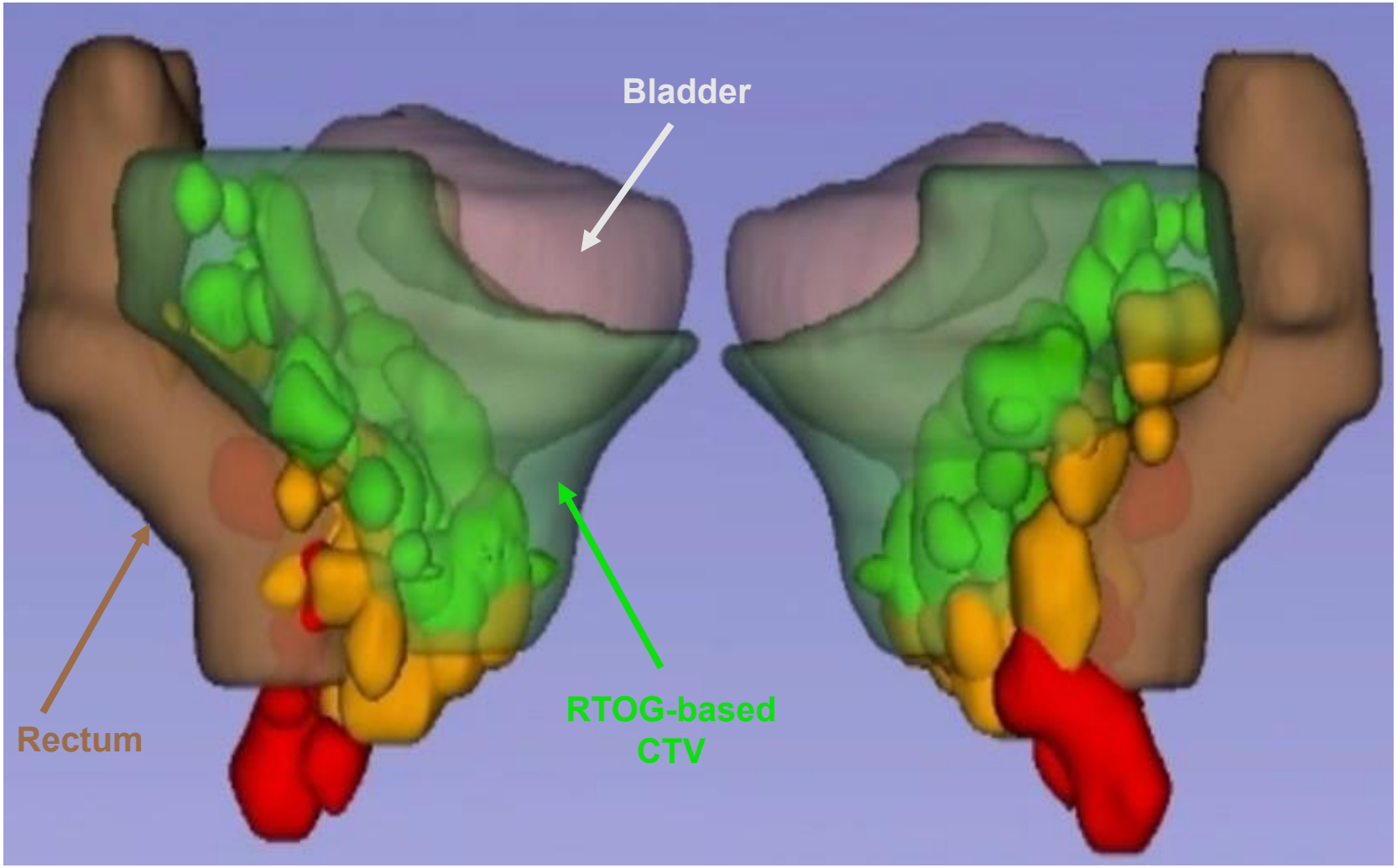
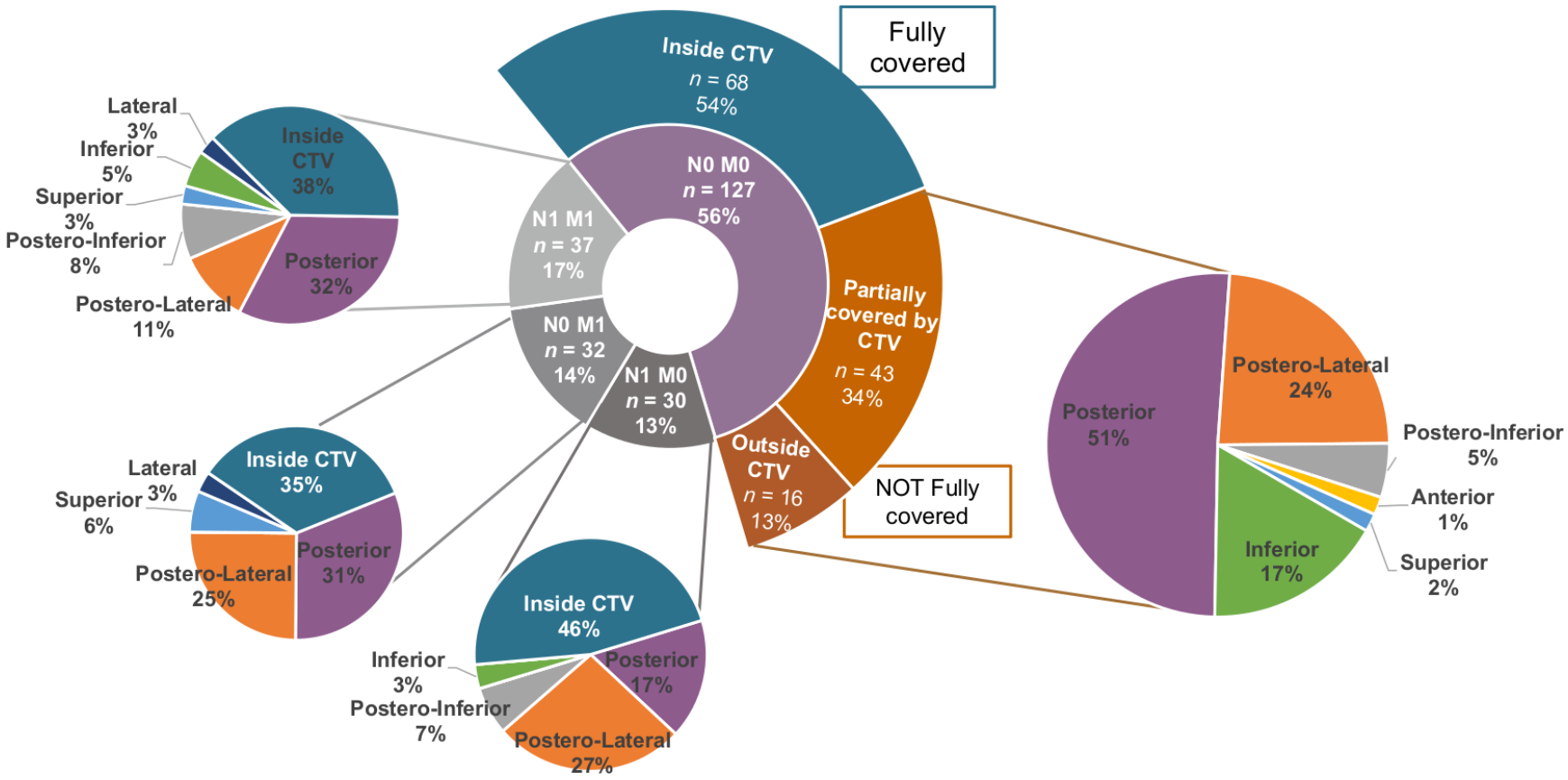


Figure 5. Results of the coverage analysis and detailed description of the location of the PSMA PET recurrences exceeding the CTV. The two central pie charts show the full cohort divided into the main cohort (miTr N0 M0 - in purple) and all sub-cohorts (in gray). The full pie charts on the sides show the location of the PSMA PET recurrences exceeding the CTV.



No. of patients	Full cohort (miTr Nx Mx) n=226	miTr N0 M0 n=127	miTr N1 M0 n=30	miTr N0 M1 n=32	miTr N1 M1 n=37	p-value
Median Age*, yr (IQR)	69.5 (64 - 73)	70 (47 - 89)	68.5 (63.3 – 76.3)	65 (61 – 74.5)	72 (68 - 76)	0.47[a]
Serum PSA ng/ml*, Median (IQR)	1.21 (0.3 – 0.6)	1.02 (0.5 – 2.18)	1.49 (1 – 2.25)	1.5 (0.52 – 4.21)	2.8 (1 – 9.24)	0.3[a]
Tumor volume (ml), Median (IQR)	0.88 (0.38 – 1.35)	0.72 (0.04 - 15)	0.89 (0.44 – 1.73)	0. 91 (0.39 – 1.34)	1.55 (0.46 – 4.6)	0.16[a]
NCCN risk group, n (%) ○ Low-risk ○ Intermediate risk ○ High risk ○ Very high ○ Not available	 ○ 9 (5) ○ 82 (44) ○ 52 (28) ○ 43 (23) ○ 40	 ○ 8 (6) ○ 54 (43) ○ 28 (22) ○ 16 (13) ○ 21	 ○ 0 (0) ○ 9 (38) ○ 7 (29) ○ 8 (33) ○ 6	 ○ 1 (3) ○ 132 (41) ○ 10 (34) ○ 6 (21) ○ 3	 ○ 0 ○ 7 (26) ○ 7 (26) ○ 13 (48) ○ 10	<0.001[b]
Surgical margin involvement, n (%) ○ No ○ Yes ○ Not available	 ○ 99 (63) ○ 57 (37) ○ 70	 ○ 58 (46) ○ 31 (24) ○ 38	 ○ 16 (84) ○ 3 (16) ○ 11	 ○ 12 (48) ○ 13 (52) ○ 7	 ○ 13 (57) ○ 10 (43) ○ 14	0.08[c]
Outcome, n (%) ○ Completely covered by CTV ○ Partially covered by CTV ○ Not covered by CTV	 ○ 107 (46) ○ 91 (41) ○ 28 (13)	 ○ 68 (53) ○ 43 (34) ○ 16 (13)	 ○ 14 (47) ○ 12 (40) ○ 4 (13)	 ○ 11 (34) ○ 17 (53) ○ 4 (13)	 ○ 14 (38) ○ 19 (51) ○ 4 (11)	0.35[c]
Location of recurrence partially or completely exceeding the CTV, n (%) ○ Total number ○ Posterior ○ Postero-lateral ○ Postero-inferior ○ Anterior ○ Superior ○ Inferior ○ Lateral	 ○ 119 (100) ○ 57 (48) ○ 34 (29) ○ 8 (7) ○ 1 (1) ○ 4 (3) ○ 13 (11) ○ 2 (2)	 ○ 59 (100) ○ 30 (51) ○ 14 (24) ○ 3 (5) ○ 1 (2) ○ 1 (2) ○ 10 (17) ○ 0	 ○ 16 (100) ○ 5 (31) ○ 8 (50) ○ 2 (13) ○ 0 ○ 0 ○ 1 (6) ○ 0	 ○ 21 (100) ○ 10 (48) ○ 8 (38) ○ 0 ○ 0 ○ 2 (10) ○ 0 ○ 1 (5)	 ○ 23 (100) ○ 12 (55) ○ 4 (17) ○ 3 (13) ○ 0 ○ 1 (4) ○ 2 (9) ○ 1 (4)	n/a
Lesion extension, n (%) ○ Rectal wall involvement ○ Bladder wall involvement	 ○ 19 (8) ○ 10 (4)	 ○ 12 (9) ○ 4 (3)	 ○ 2 (7) ○ 1 (3)	 ○ 1 (3) ○ 0	 ○ 4 (10) ○ 5 (13)	0.23[c]

Table 1. Clinical and demographic characteristics of all patients and all cohorts. Location and extension of the tumor recurrence on PSMA PET of the full cohort and sub-cohorts. Age and PSA are at time of PET. The percentage was calculated on the total number of patients with the data available in the selected category. [a] One-way ANOVA; [b] Spearman ρ correlation matrix; [c] chi-square test.

	miTr N0 M0 (n=127)	COMPLETELY coveredby CTV (n=68)	PARTIALLY covered by CTV (n=43)	NOT covered by CTV (n=16)	p-value
Number of patients (%)	127 (100)	68 (54)	43 (34)	16 (13)	n/a
Median Age, yr (IQR)	70 (64 - 73)	69.5 (62 - 72)	70 (67 - 75)	68.5 (66.3 – 75.3)	0.14[a]
Serum PSA ng/ml, Median (IQR)	1.02 (0.5 – 2.18)	1.11 (0.5 – 2.2)	1.09 (0.46 – 2.63)	0.84 (0.62 – 1.11)	0.26[a]
Tumor volume (ml), Median (IQR)	0.72 (0.38 – 1.35)	0.57 (0.36 – 1.13)	1.01 (0.49 - 67)	0.68 (0.37 – 0.96)	0.12[a]
NCCN risk group, n (%) ○ Low-risk ○ Intermediate risk ○ High risk ○ Very high ○ Not available	 ○ 8 (8) ○ 54 (51) ○ 28 (26) ○ 16 (15) ○ 21	 ○ 7 (10) ○ 26 (38) ○ 12 (18) ○ 9 (13) ○ 14	 ○ 0 (0) ○ 19 (44) ○ 12 (28) ○ 5 (12) ○ 7	 ○ 1 (6) ○ 8 (50) ○ 4 (25) ○ 2 (13) ○ 1	0.38[b]
Surgical margin involvement, n (%) ○ No ○ Yes ○ Not available	 ○ 58 (65) ○ 31 (35) ○ 38	 ○ 21 (45) ○ 26 (55) ○ 21	 ○ 20 (69) ○ 9 (31) ○ 16	 ○ 12 (92) ○ 1 (8) ○ 4	0.04[c]
Location of recurrence partially or completely exceeding the CTV, n (%) ○ Total number ○ Posterior ○ Postero-lateral ○ Postero-inferior ○ Anterior ○ Superior ○ Inferior	 ○ 59 (100) ○ 30 (52) ○ 14 (24) ○ 3 (5) ○ 1 (2) ○ 1 (2) ○ 10 (14)	○ n/a	 ○ 43 (100) ○ 25 (58) ○ 10 (23) ○ 1 ○ 1 (2) ○ 1 (2) ○ 5 (10)	 ○ 16 (100) ○ 5 (31) ○ 4 (25) ○ 2 (13) ○ 0 ○ 0 ○ 5 (31)	n/a
Local extension, n (%) ○ Rectal wall involvement ○ Bladder wall involvement	 ○ 12 (9) ○ 4 (3)	 ○ 1 (1) ○ 4 (6)	 ○ 5 (12) ○ 0	 ○ 6 (38) ○ 0	0.002[c]

Table 2: Clinical characteristics and outcome analysis for the miTr N0 M0 cohort.
Age and PSA are at time of PET. The percentage was calculated on the total number of patients with the data available in the selected category. [a] One-way ANOVA; [b] Spearman ρ correlation matrix; [c] chi-square test.

KEY POINTS

QUESTION: Are the clinical target volumes (CTV) used for salvage radiation treatment of the prostate bed covering the full extent of disease based on PSMA PET findings?

PERTINENT FINDINGS: In patients experiencing PSA persistence or biochemical recurrence post-RP with disease limited to the prostate bed on PSMA PET, RTOG-based CTV for salvage radiation therapy leave 13% of the recurrences untreated, and 34% partially treated. Most of the recurrences not covered by the CTV extend beyond the posterior and inferior aspect of the prostate bed, whereas the anterior and superior borders are rarely involved highlighting the need for CTV redefinition with the use of PSMA PET.

IMPLICATIONS FOR PATIENT CARE: Current guidelines for salvage radiation therapy to the prostate bed leave 13% of lesions untreated and 34% partially treated. The advantage of using PSMA PET data to redefine these contouring guidelines is twofold: it would increase coverage of the tumor recurrences and reduce the unnecessary exposure of healthy tissues to toxic radiation.

REFERENCES

1. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst.* 2006;98:715-717.

2. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *Jama.* 2005;294:433-439.

3. Freedland SJ, Rumble RB, Finelli A, et al. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol.* 2014;32:3892-3898.

4. Zaorsky NG, Calais J, Fanti S, et al. Salvage therapy for prostate cancer after radical prostatectomy. *Nat Rev Urol.* 2021;18:643-668.

5. Michalski JM, Lawton C, El Naqa I, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2010;76:361-368.

6. Poortmans P, Bossi A, Vandeputte K, et al. Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. *Radiother Oncol.* 2007;84:121-127.

7. Sidhom MA, Kneebone AB, Lehman M, et al. Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. *Radiother Oncol.* 2008;88:10-19.

8. Wiltshire KL, Brock KK, Haider MA, et al. Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. *Int J Radiat Oncol Biol Phys.* 2007;69:1090-1099.

9. Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol.* 2007;177:540-545.

10. FDA Approves First PSMA-Targeted PET Drug. *J Nucl Med.* 2021;62:11n.

11. Valle L, Shabsovich D, de Meerleer G, et al. Use and Impact of Positron Emission Tomography/Computed Tomography Prior to Salvage Radiation Therapy in Men with Biochemical Recurrence After Radical Prostatectomy: A Scoping Review. *Eur Urol Oncol.* 2021;4:339-355.

12. Eder M, Schäfer M, Bauder-Wüst U, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. *Bioconjug Chem.* 2012;23:688-697.

13. Halpern BS, Dahlbom M, Quon A, et al. Impact of patient weight and emission scan duration on PET/CT image quality and lesion detectability. *J Nucl Med.* 2004;45:797-801.

14. Fendler WP, Eiber M, Beheshti M, et al. (68)Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* 2017;44:1014-1024.

15. Eiber M, Herrmann K, Calais J, et al. Prostate cancer molecular imaging standardized evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. *J Nucl Med.* 2018;59:469-478.

16. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging.* 2012;30:1323-1341.

17. Rowe LS, Harmon S, Horn A, et al. Pattern of failure in prostate cancer previously treated with radical prostatectomy and post-operative radiotherapy: a secondary analysis of two prospective studies using novel molecular imaging techniques. *Radiat Oncol.* 2021;16:32.

18. Calais J, Czernin J, Cao M, et al. (68)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. *J Nucl Med.* 2018;59:230-237.

19. Ghadjar P, Hayoz S, Bernhard J, et al. Dose-intensified Versus Conventional-dose Salvage Radiotherapy for Biochemically Recurrent Prostate Cancer After Prostatectomy: The SAKK 09/10 Randomized Phase 3 Trial. *Eur Urol.* 2021;80:306-315.

20. Qi X, Li HZ, Gao XS, et al. Toxicity and Biochemical Outcomes of Dose-Intensified Postoperative Radiation Therapy for Prostate Cancer: Results of a Randomized Phase III Trial. *Int J Radiat Oncol Biol Phys.* 2020;106:282-290.

21. Horsley PJ, Koo CM, Eade T, et al. nnMapping of local recurrences after radical prostatectomy using 68-Gallium-PSMA-PET/CT: Implications for post-prostatectomy radiotherapy clinical target volumes. *Int J Radiat Oncol Biol Phys.* 2022.

22. Beck M, Sassowsky M, Schär S, et al. Adherence to Contouring and Treatment Planning Requirements Within a Multicentric Trial: Results of the Quality Assurance of the SAKK 09/10 trial. *Int J Radiat Oncol Biol Phys.* 2022;113:80-91.

23. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. *J Nucl Med.* 2007;48:932-945.

24. Daryanani A, Turkbey B. Recent Advancements in CT and MR Imaging of Prostate Cancer. *Semin Nucl Med.* 2022;52:365-373.

25. Calais J, Armstrong WR, Kishan AU, et al. Update from PSMA-SRT Trial NCT03582774: A Randomized Phase 3 Imaging Trial of Prostate-specific Membrane Antigen Positron Emission Tomography for Salvage Radiation Therapy for Prostate Cancer Recurrence Powered for Clinical Outcome. *Eur Urol Focus.* 2021;7:238-240.

26. Spohn SKB, Farolfi A, Schandeler S, et al. The maximum standardized uptake value in patients with recurrent or persistent prostate cancer after radical prostatectomy and PSMA-PET-guided salvage radiotherapy-a multicenter retrospective analysis. *Eur J Nucl Med Mol Imaging.* 2022;50:218-227.

miTr Nx Mx cohort (n=226)	COMPLETELY covered by CTV (n=107)	NOT covered by CTV (n=28)	PARTIALLY covered by CTV (n=91)	p-value
Median Age*, yr (IQR)	69 (63 - 73)	69 (67 – 76.3)	70 (63.25 - 75)	0.38[a]
Serum PSA ng/ml*, Median (IQR)	1.40 (0.6 – 2.4)	0. 92 (0.59 – 1.76)	1.3 (0.57 – 4.25)	0.27[a]
Tumor volume (ml), Median (IQR)	0.7 (0.37 – 1.33)	0.7 (0.37 – 1.31)	1.09 (0.51 – 2.83)	0.03[a]
NCCN risk group, n (%)** ○ Low-risk ○ Intermediate risk ○ High risk ○ Very high ○ Not available	 ○ 8 (9) ○ 35 (41) ○ 23 (27) ○ 19 (22) ○ 21	 ○ 1 (4) ○ 14 (54) ○ 7 (27) ○ 4 (15) ○ 2	 ○ 0 ○ 32 (43) ○ 22 (30) ○ 20 (27) ○ 17	n/a
Surgical margin involvement, n (%)** ○ No ○ Yes ○ Not available	 ○ 42 (59) ○ 29 (41) ○ 36	 ○ 19 (79) ○ 5 (21) ○ 4	 ○ 38 (62) ○ 23 (38) ○ 31	0.15[b]
Location of recurrence partially or completely exceeding the CTV, n (%) ○ Posterior ○ Postero-lateral ○ Postero-inferior ○ Anterior ○ Superior ○ Inferior ○ Laterally	n/a	○ 10 (36) ○ 7 (25) ○ 4 (14) ○ 0 ○ 0 ○ 0 ○ 7 (25) ○ 0	○ 47 (52) ○ 27 (30) ○ 4 (4) ○ 1 (1) ○ 4 (4) ○ 5 (5) ○ 2 (2)	n/a
Local organs involvement, n (%) ○ Rectal wall involvement ○ Bladder wall involvement	 ○ 1 (1) ○ 8 (8)	 ○ 9 (32) ○ 0	 ○ 9 (10) ○ 2 (2)	0.001[c]

Supplementary Table 1. Clinical characteristics and location of recurrences based on the three outcomes in the whole cohort (miTr Nx Mx). Age and PSA are at time of PET. The percentage was calculated on the total number of patients with the data available in the selected category. [a] One-way ANOVA; [b] Spearman ρ correlation matrix; [c] chi-square test.