Clinical and Translational Radiation Oncology 32 (2022) 41–47

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Defining radio-recurrent intra-prostatic target volumes using PSMA-targeted PET/CT and multi-parametric MRI

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ARTICLE INFO

Keywords:
Prostate cancer
PSMA PET/CT
MRI
Radio-recurrence

ABSTRACT

Purpose: Our purpose was to evaluate intra-prostatic cancer volumes for salvage radiotherapy in men with recurrent prostate cancer confined to the prostate post-primary radiotherapy using mpMRI and 18F-DCFPyL PET/CT (PET).

Methods: Men with biochemical failure post-primary radiotherapy were enrolled in a multi-centre trial investigating mpMRI and PET. All men with isolated intra-prostatic recurrence are included in this secondary analysis. The intra-prostatic gross tumour volume (GTV) was manually delineated on mpMRI and was also delineated on PET using three methods: 1. manually, 2. using a 30% threshold of maximum intra-prostatic standard uptake value (SUVmax), and 3. using a 67% threshold of this SUVmax. Clinical target volumes (CTV) including expansions on each GTV were generated. Conformity indices were performed between the mpMRI CTV and each PET CTV. Correlation with biopsy and clinical outcomes were performed.

Results: Of the 36 men included, 30 (83%) had disease in two quadrants or less using the combination of mpMRI and PET. Mean target volume (union of CTV on mpMRI and CTV manually delineated on PET) was 12.2 cc (49% of prostate gland volume). 12/36 (33%) men had a biopsy. Per-patient sensitivity was 91% for mpMRI and 82% for PET.

Conclusions: mpMRI and PET provide complementary information for delineation of intra-prostatic recurrent disease. Union of CTV on mpMRI and PET is often less than 50% of the prostate, suggesting this imaging could help define a target for focal salvage therapy.

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https://doi.org/10.1016/j.ctro.2021.11.006
Received 13 September 2021; Received in revised form 8 November 2021; Accepted 8 November 2021
Available online 14 November 2021

Introduction:

Up to 35% of prostate cancer patients treated with dose-escalated external beam radiotherapy (EBRT) experience biochemical failure (BF) by Phoenix Criteria [1] within 10 years [2]. Local salvage treatment such as radical prostatectomy, brachytherapy, cryoablation, high-intensity focused ultrasound (HIFU), and stereotactic body radiotherapy (SBRT) provide durable biochemical control in only half of these patients and are associated with severe genitourinary or gastrointestinal toxicity in up to 25% of cases [3]. As a consequence, local salvage treatment is infrequently used, and most patients with recurrent disease are given androgen deprivation therapy (ADT) or are placed under observation [4–5]. Next generation imaging techniques may improve local salvage therapy outcome through more precise intra-prostatic recurrence targeting (potentially lowering toxicity) and early identification of men with metastatic disease (potentially enabling better patient selection for long-term control) [6–7].

Focal salvage therapy that targets only part of the prostate gland has been investigated, with the goal of decreasing toxicity compared to whole-gland re-irradiation [8]. Until recently, multi-parametric magnetic resonance imaging (mpMRI) has been the preferred imaging modality for target delineation, but may miss small lesions and underestimate disease volume in both the primary and post-radiotherapy settings [9–11]. Prostate-specific membrane antigen (PSMA)-targeted positron emission tomography/ computed tomography (PET/CT) may improve focal salvage outcome through improved intra-prostatic target delineation with the added benefit of improved patient selection (by excluding men with distant disease). A prospective, single-arm study showed PSMA-targeted PET/CT detected extra-prostatic disease in more patients with BF after primary radiotherapy compared to conventional imaging [12]. Also, prior to primary prostatectomy, the combination of PSMA-targeted PET/CT and mpMRI has increased sensitivity for the detection of intra-prostatic disease compared to either technique alone, suggesting a role for target delineation [13–14]. To our knowledge, no study to date has evaluated the combination of PSMA-targeted PET/CT and mpMRI for target volume delineation in men with locally recurrent prostate cancer after radiotherapy.

Methods

PICS (NCT02793284) is a multi-center prospective trial of 79 men with BF after primary EBRT or brachytherapy for localized prostate cancer [12]. Ethics approval was obtained from the Ontario Cancer Research Ethics Board and all patients signed informed consent. Eligibility criteria included localized T1-2 prostate cancer with zero or one high-risk feature (prostate-specific antigen [PSA] greater than 20 ng/mL or Gleason Grade 8) treated with primary radiotherapy, with or without ADT. Patients were required to undergo conventional imaging prior to PSMA-targeted PET/CT, including contrast-enhanced CT of the abdomen and pelvis, whole body bone scan (BS), and mpMRI of the pelvis, including T1-weighted (T1W), T2-weighted (T2W), diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), and dynamic contrast-enhanced (DCE) sequences. All men had 2-(3-{1-carboxy-5-[(6-[18F]fluoropyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioicacid (18F-DCFPyL) PET/CT. 333 MBq (9 mCi) +/- 10% 18F-DCFPyL IV was administered followed by an uptake period of 60 min (+/- 10 min) and imaging from the skull vertex to the mid-thighs. The PET/CT images were then transferred to a central database (Quantitative Imaging for Personalized Cancer Medicine) for analysis. All PSMA-targeted PET/CT scans were double read by a local and a central (LE) nuclear medicine physician. When needed, a third nuclear medicine physician provided an additional read for the purpose of obtaining consensus. Each lesion detected was classified as being either benign (definitely not malignant, probably not malignant, or equivocal) or malignant (probably malignant or definitely malignant). Each mpMRI was reported by a local radiologist experienced in prostate mpMRI. Men were considered to have localized recurrence if they had intra-prostatic recurrence detected on mpMRI, PET/CT, or both and no extra-prostatic disease on both mpMRI and PET/CT. Subjects were excluded if mpMRI were not uploaded to the central database or if an endorectal coil was used for mpMRI, to limit co-registration error.

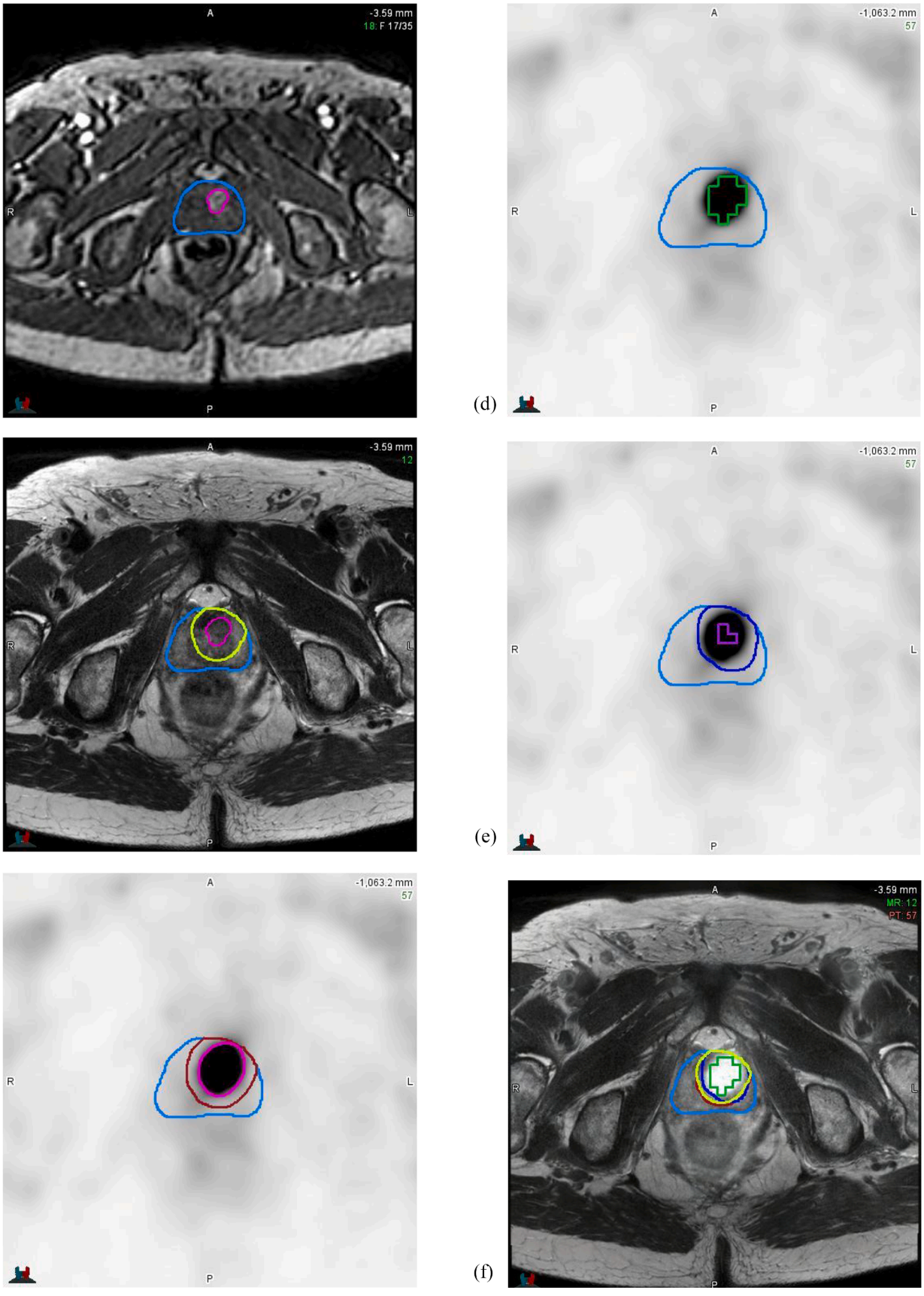
We hypothesized that more than 50% of men have involvement of either one or two prostate gland quadrants (left superior, right superior, left inferior and right inferior) based on the union of gross tumour on mpMRI and PET/CT. MIM was used to perfom rigid co-registration of mpMRI and PET/CT images. The prostate gland was contoured using fusion of the T2W MRI sequence and CT. As no method for target delineation has been histologically validated in the radio-recurrent setting, we delineated targets using methods that have been validated in the primary setting, as shown in Fig. 1 [15–17].

Multiple target volumes were generated for each patient using both mpMRI and PET/CT images. The GTV was delineated manually on the mpMRI images (T2W, DWI, ADC, and DCE sequences) without reference to PET/CT results (referred to as GTV MRI). If volumes differed between sequences, the union of volumes on all sequences was used. Lesion delineation was performed by a radiation oncologist (WL) with reference to mpMRI reports. In the case of uncertainty, contours were reviewed by a radiologist (ZK), for example, when the radiology report was not specific in terms of the lesion size, location, or appearance. The CTV included an 8 mm expansion of the GTV MRI, bounded by the prostate gland (referred to as CTV MRI). This method has been shown to include 95% of disease based on histopathology in the primary prostatectomy setting [15]. The GTV was manually drawn on the PET/CT using minimum to maximum standardized uptake value (SUV) scaling of 0-5 (referred to as GTV PET manual) without reference to the mpMRI and included only lesions that were classified as either definitely malignant or probably malignant by nuclear medicine physicians. It has been previously shown that in the primary setting, using a primary radical prostatectomy reference, this method produces a median sensitivity of 86–89% and median specificity of 73–92% [17]. Lesion delineation was performed by WL. In the case of uncertainty, contours were reviewed by a nuclear medicine physician (IR). The CTV included a 5 mm expansion on the GTV PET Manual, limited to the prostate gland (referred to as CTV PET Manual). This margin was chosen because it is used in many cancers to target microscopic disease and has been evaluated in a prospective trial for salvage brachytherapy [18].

We also explored PET/CT volumes using a threshold of the maximum SUV (SUVmax). Volumes generated using a 20% threshold of the maximum intra-prostatic SUV were too large for focal therapy and were dismissed. We produced the GTV PET 30% using a 30% threshold of the intra-prostatic disease SUVmax. No margin was added for the CTV PET 30% as there is good concordance in the primary setting with histologic volumes [19]. The GTV PET 67% was generated using a 67% threshold of the intra-prostatic disease SUVmax. The GTV PET 67% was modified to exclude discreet regions of SUV spillage from the bladder into the prostate. An 8.5 mm expansion limited to the prostate gland was included for CTV PET 67%. This method has been shown to have sensitivity and specificity of 95% and 76% respectively based on whole-mount histopathology in the primary prostatectomy setting [16]. Union volumes of the CTV MRI and each CTV PET were generated. All target volumes were compared.

Involvement by quadrant was based on the GTV MRI, GTV PET Manual, or union of both volumes. Dice similarity coefficient (DICE), Hausdorff distant (HD), mean distance to agreement (MDA), and Jaccard index were performed for the CTV MRI and each CTV PET. Single factor analysis of variance and post-hoc Tukey test were performed between CTV comparisons for each of the DICE, HD, MDA and Jaccard index.

Clinical management was prospectively captured as part of the PICS clinical trial. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated where post-PET/CT biopsy information was available. We also report oncologic



(caption on next page)

Fig. 1. Rigidly co-registered mpMRI and PSMA-targeted PET/CT axial slices. Prostate was contoured on mpMRI co-registered with CT. GTV and CTV were independently contoured on mpMRI or PSMA-targeted PET/CT, blinded to the other modality. Minimum to maximum SUV scaling of 0–5 was used for PET/CT. 1a. Axial slice of DCE MRI image. Blue - Prostate. Pink – GTV MRI. 1b. Axial slice of T2W image. Blue - Prostate. Pink – GTV MRI. Light green – CTV MRI (GTV MRI + 8 mm expansion within the prostate). 1c. Co-registered PET axial slice. Minimum to maximum SUV scaling of 0–5. Blue – prostate (contoured on mpMRI co-registered with CT). Pink – GTV PET Manual. Red – CTV PET Manual (GTV Manual + 5 mm within prostate). 1d. Co-registered PET axial slice. Blue – prostate. Dark green – GTV PET 30% = CTV PET 30%. 1e. Co-registered PET axial slice. Blue – prostate. Purple – GTV PET 67%. Dark blue – CTV PET 67% (GTV PET 67% + 8.5 mm expansion within prostate). 1f. Axial slice of T2W image co-registered with PET. Minimum to maximum SUV scaling 0–5. Light green – CTV MRI. Red – CTV PET Manual. Dark green – CTV PET 30%. Dark blue – CTV PET 67%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

outcomes for patients from this cohort who were treated with focal salvage brachytherapy.

Results

40/79 men (51%) had isolated intra-prostatic recurrence. Forty-two men had isolated intra-prostatic recurrence on mpMRI and 38 on PET/CT. 10/42 men with isolated intra-prostatic recurrence on mpMRI had extra-prostatic disease on PET/CT and were excluded. None of the 38 men with isolated intra-prostatic recurrence on PET/CT had extra-prostatic disease on mpMRI. Four men either did not have accessible mpMRI or had an endorectal coil for the mpMRI and were excluded. Of the 36 men included in this study, isolated recurrence was detected on mpMRI alone (n = 2), PET/CT alone (n = 6), or mpMRI and PET/CT (n = 28). Patient characteristics are shown in Table 1. The median PSA at enrolment was 4.7 ng/mL (range 2.1–65.1) and median PSA doubling time (PSADT) was 14.5 months (range 1.9 to 48.6 months). PET/CT was performed a median of 10 days after the mpMRI.

Involvement by prostate gland quadrant is shown in Fig. 2. 30/36 men (83%, 95% confidence interval 68–92%) had involvement of two quadrants or less. 28/36 (78%) men had at least one lesion detected on the combination of mpMRI and PET/CT. Among these men, the mean prostate volume was 24.8 cc. Target volumes are depicted in Fig. 3 and the agreement between volumes is shown in Table 2. There was significant variation between volumes using DICE, HD, MDA, and Jaccard index (p less than 0.005). The post-hoc Tukey test showed the CTV PET Manual had better agreement with the CTV MRI compared to the CTV PET 30% (p less than 0.05). Also, the CTV PET Manual trended towards better agreement with the CTV MRI compared to CTV PET 67% (p greater than 0.05).

Of 6 men with lesions on PET/CT but not mpMRI, all had a single intra-prostatic lesion with a mean SUVmax 4.1 and mean GTV PET Manual volume of 1.3 cc. Of 2 men with lesions on mpMRI but not PET/CT, both had a single intra-prostatic lesion with CTV MRI of 0.5 cc and 0.9 cc respectively.

12/36 men had a biopsy and 11/12 had biopsy-proven recurrence, of which 8 had lesions classified as malignant on both mpMRI and PET/CT, 2/11 on mpMRI alone, and 1/11 on PET/CT alone. The two patients with lesions classified as malignant on mpMRI alone both had visible lesions not classified as malignant on PET/CT. One lesion had SUVmax of 2.5 and was reported to be definitely not malignant. The other lesion had SUV max of 7.5 and was reported to be equivocal. The per-patient sensitivity was 91% for mpMRI-detected lesions, 82% for PET/CT-detected lesions, and 100% for lesions detected on either mpMRI or PET/CT. On a per-lobe (right or left) basis, the sensitivity, specificity, PPV and NPV for mpMRI were 83%, 91%, 91%, and 83% respectively; 75%, 82%, 82%, and 75% for PET/CT respectively; and 92%, 73%, 79%, and 89% for the combination of mpMRI and PET/CT.

Patient management after imaging in the PICS trial was previously reported [20]. In this subset of men with isolated local recurrence, within 6 months of imaging, 4 men received focal salvage high dose-rate brachytherapy (sHDR) without ADT (Table 3). Focal sHDR was based on mpMRI and transrectal ultrasound using cognitive fusion or deformable registration. At a median follow-up of 32 months, 2/4 patients (50%) had a second BF by Phoenix Criteria. Both patients with second BF had an initial PSA response, with PSA nadirs of 0.7–1.0 after sHDR. One patient experienced BF 9 months after sHDR. He was not interested in further salvage therapy and received intermittent ADT. The other patient experienced BF 25 months after sHDR. At 32 months after sHDR, his PSA was 4.5 and he received repeat PET/CT. He was found to have an isolated local recurrence again at the site of the initial recurrence.

Table 1
Baseline patient characteristics.

Characteristic	Statistic	Result
N		36
Age	Mean (std dev)	74.8 (7.9)
	Median (range)	76 (55, 88)
Initial T Stage	N (%)	
	T1	25 (69)
	T2	1 (3)
	T2a	6 (17)
	T2b	3 (8)
	T2c	1 (3)
Initial Gleason Score	N (%)	
	3 + 3	13 (36)
	3 + 4	15 (42)
	4 + 3	8 (22)
Initial PSA	Mean (std dev) Median (range)	9.5 (11.0) 7.4 (1.8–71.0)
Initial NCCN risk group	N (%)	
	Low risk	11 (31)
	Intermediate risk	24 (67)
	High risk	1 (3)
PSA at enrolment	Mean (std dev)	8.2 (10.6)
	Median (range)	4.7 (2.1–65.1)
PSA Doubling Time, MSKCC (months)	Mean (std dev)	17.3 (10.6)
	Median (range)	14.5 (1.9, 48.6)
Previous Radiotherapy	N (%)	
	EBRT	22 (61)
	Brachytherapy	14 (39)

Discussion

Most patients with recurrent prostate cancer after primary radiotherapy are either observed or are given palliative ADT; rarely is salvage therapy offered [4–5]. Concerns regarding treatment-related toxicity and identification of localized recurrence likely contribute to underutilization of salvage treatment. A *meta*-analysis of salvage therapies reported a pooled severe GU toxicity rate of 21% for salvage prostatectomy with slightly lower rates for SBRT or brachytherapy [3]. In a prospective study of whole-gland salvage low dose-rate brachytherapy (sLDR), 14% of patients had late grade 3 toxicity [21]. Focal salvage, which spares a portion of the prostate, may be associated with less toxicity; however, an optimal strategy for target delineation has not been established. Often mpMRI is used to guide focal salvage [22–25], but in salvage prostatectomy studies, mpMRI was found to underestimate the true volume of disease recurrence [9–10].

We found that the union of GTV MRI and GTV PET Manual included two quadrants or less of the prostate gland in the majority of men (83%) with isolated intra-prostatic radio-recurrent disease, suggesting a role for targeted salvage therapy. We delineated the target disease using both mpMRI and PET/CT with methods that have been histologically validated in the primary treatment setting. Gibson et al. showed that an 8 mm expansion of a mpMRI-delineated GTV was required to achieve 95%

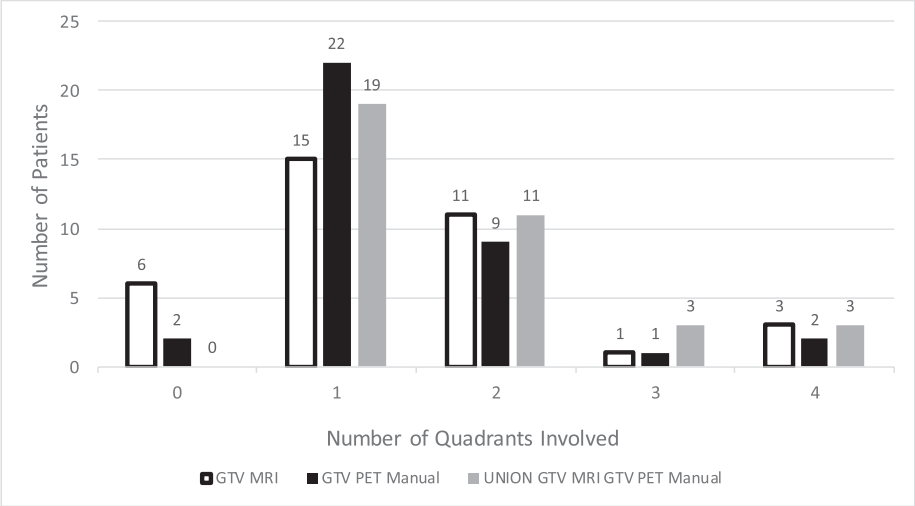


Fig. 2. Number of quadrants involved as detected by mpMRI, PET/CT, and both modalities.

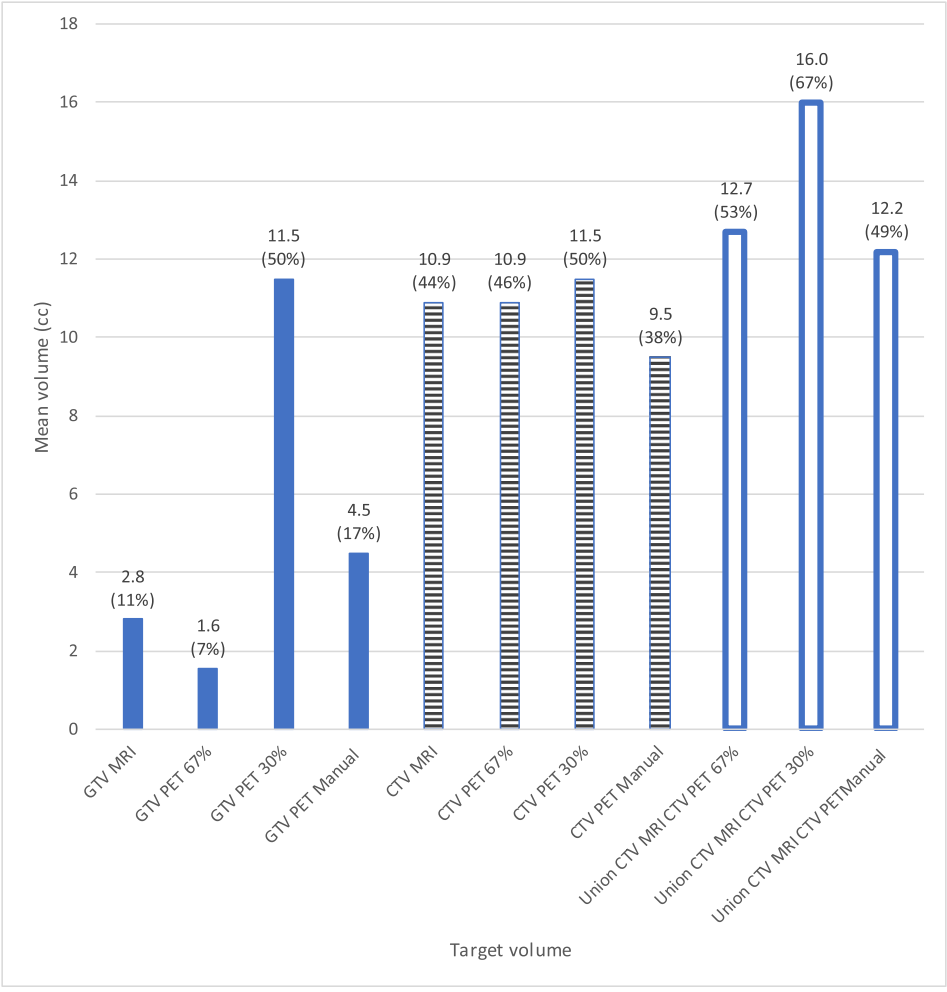


Fig. 3. Mean volume and mean percentage of prostate volume (bracketed) of contoured target volumes.

median sensitivity and that this spared 47–72% of the prostate gland [15]. Alfano et al. showed that an 8.4 mm expansion of a PSMA-targeted PET/CT-delineated GTV using a 67% threshold of intra-prostatic SUVmax achieved 95% mean sensitivity and spared 63% of the prostate gland [16]. Zamboglou et al. showed that using manual delineation for the GTV on PET/CT achieved a median sensitivity and specificity of 86–89% and 73–92% respectively, while using semi-automatic contours with a 30% threshold of intra-prostatic SUVmax achieved median sensitivity and specificity of 83% and 90% respectively [17].

PET/CT and mpMRI appear to be complementary for detecting

Table 2
Agreement between CTV MRI and PET/CT-derived CTV.

	Mean DICE (95% CI)	Mean HD (mm; 95% CI)	Mean MDA (mm; 95% CI)	Mean Jaccard index (95% CI)
CTV PET 67% and CTV MRI	0.70 (0.65–0.75)	11.9 (9.5–14.4)	2.3 (1.7–2.9)	0.57 (0.51–0.63)
CTV PET 30% and CTV MRI	0.53 (0.47–0.59)	15.1 (12.8–17.4)	3.7 (2.9–4.5)	0.39 (0.32–0.45)
CTV PET Manual and CTV MRI	0.75 (0.69–0.81)	8.3 (6.0–10.6)	1.6 (1.0–2.3)	0.64 (0.57–0.71)

recurrent lesions. PET/CT combined with mpMRI had higher per-lobe sensitivity (92%) and NPV (89%) compared with either modality alone among patients with confirmatory biopsy. Furthermore, 6 patients had lesions detected on PET/CT alone and 2 patients on mpMRI alone. It has been shown that both mpMRI and PSMA-targeted PET/CT potentially miss radio-recurrent lesions. Dinis Fernandes et al. showed that in 5/21 patients with radio-recurrence, radiologist contours on mpMRI did not visually overlap with step-section pathology [10]. Similarly, for PSMA-targeted PET/CT, Pfister et al. reported per-lobe sensitivity and NPV of 81% and 32% respectively based on salvage prostatectomy in patients previously treated with RT or HIFU [26]. In our study, even with combined PET/CT and mpMRI, the false negative rate per-lobe was 11%. Based on the improved but still imperfect sensitivity and NPV of combined PET/CT and mpMRI compared to either modality alone, we recommend biopsy in addition to co-registered PET and mpMRI for detecting recurrence prior to focal salvage therapy.

The optimal method for delineation of locally radio-recurrent prostate cancer based on PET and mpMRI is not known. We explored agreement between volumes using several metrics. DICE and Jaccard indices are overlap metrics, with range 0 to 1 [27–28]. HD is the maximum distance between two surfaces and MDA is the mean distance between two surfaces, with smaller distances representing better surface agreement. CTV PET Manual had better agreement with CTV MRI than CTV PET 30% according to the DICE, HD, MDA and Jaccard index. These metrics also showed that the CTV PET Manual trended towards better agreement with CTV MRI compared to CTV PET 67%. This suggests the union of CTV MRI and CTV PET Manual should be further investigated as a method for target delineation for focal salvage, either with comparison to salvage prostatectomy histopathology or with prospective clinical trials.

The ultimate success of local salvage therapy depends on identification of men with localized intra-prostatic recurrence; however, identification of these patients has been challenging using conventional imaging. In RTOG-0526, trialists aimed to select patients with a high likelihood of localized recurrence. Inclusion criteria included biopsy-proven local recurrence, BF at least 30 months after EBRT, initial low or intermediate-risk disease, pre-salvage PSA of 10 or less, and negative restaging BS and CT abdomen/ pelvis [21]. However, despite these inclusion criteria, the 10-year BF rate after whole-gland sLDR was 46%, compared to the 10-year local failure rate of 5%, suggesting many patients may have had undetected metastatic disease at time of salvage [29]. PSMA PET/CT improves selection of patients for salvage therapy. In PICS, we found that PSMA PET/CT detected extra-prostatic disease in twice as many patients (39% vs. 19%) compared to the combination of bone scan; CT of the chest, abdomen and pelvis; and mpMRI of the pelvis [12].

It is not currently known if improved patient selection with PSMA-targeted PET/CT also improves oncologic outcomes for patients with local radio-recurrence who undergo salvage therapy. Encouragingly, the EMPIRE-1 randomized trial showed improved 3-year event-free survival in men with BF after prostatectomy who received PET-directed salvage treatment compared to salvage treatment based on conventional imaging [30]. Similar to our results after sHDR, van Son et al. reported biochemical disease-free survival of 51% at a median follow-up of 31 months in 50 locally radio-recurrent patients who underwent ultra-focal sHDR to a dose of 19 Gy in one fraction [18]. GTV was delineated using mpMRI and PET was used to confirm the location. A 5mm CTV margin was used. 22/26 patients with second BF had intra-prostatic recurrence. The authors suggested the high local recurrence rate may be secondary to the target volumes and dose fractionation. They discussed that a 5 mm margin to MRI-derived GTV may not be sufficient. In another study, 25 men with isolated local radio-recurrent disease and concordant mpMRI and PSMA-targeted PET/CT findings underwent focal salvage SBRT [31]. Freedom from BF was 80% at 2 years. Ultimately, randomized studies evaluating oncologic outcomes after salvage therapy for patients with radio-recurrent prostate cancer are needed.

Our study has limitations. Pathologic confirmation of the mpMRI and PSMA targeted PET/CT-derived volumes was not available for all patients. We did, however, find excellent concordance when confirmatory biopsies were available (11/36 men). Further, our analysis included mostly patients with initial low or intermediate risk prostate cancer (97%), PSA less than 10 prior to imaging (89%), and PSADT of more than 6 months (89%). As such, these results may not apply to other populations.

The strengths of this study include the novel analysis of radio-recurrent intra-prostatic volumes using both PSMA-targeted PET/CT and mpMRI; image acquisition through a prospective, multi-center clinical trial; and correlation with biopsy results.

Conclusions

mpMRI and PSMA-targeted PET/CT provide complementary information for delineation of intra-prostatic recurrent disease. Union of CTV on MRI and PET included less than 50% of the gland in most men, suggesting use of this imaging could help define focal salvage therapy.

Financial disclosures

Dr. Peter Chung reports other from Sanofi, personal fees from AbbVie, other from Tersera, personal fees from Astra Zeneca, personal fees from Boston Scientific, personal fees from Verity, outside the submitted work.

Dr. Glenn Bauman reports grants from Ontario Institute for Cancer Research and a CARO ACURA grant, during the conduct of the study.

Dr. Katherine Zukotynski reports grants from Ontario Institute for Cancer Research, Prostate Cancer Canada and the Canadian Cancer Society, during the conduct of the study.

Table 3
Characteristics and oncologic outcomes for patients who underwent focal salvage high dose rate brachytherapy without systemic therapy.

NCCN Risk Group	Previous radiation	Pre-salvage PSA	PSA Doubling time (months)	Dose	Fractions	Follow-up (months)	Local failure	Biochemical failure
Low	Brachytherapy	2.8	4.5	27 Gy	2	32.1	no	yes
Intermediate	EBRT	3.2	13.5	27 Gy	2	31.0	no	no
Low	Brachytherapy	3.4	36.4	27 Gy	2	34.5	no	no
Low	Brachytherapy	3.4	7	27 Gy	2	31.4	yes	yes

Support

This study was funded by grants from the Ontario Institute for Cancer Research (OICR #CTI-PICs-LHRI) and the Canadian Association of Radiation Oncology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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