Original Article

# Contribution of $^{68}$Ga-PSMA PET/CT to targeting volume delineation of prostate cancer treated with conformal radiation therapy: Which SUV threshold is appropriate?

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## ABSTRACT

**Introduction:** Prostate-specific membrane antigen (PSMA) has been demonstrated as a promising tool for specific imaging of prostate cancer (PCa) via positron emission tomography-computed tomography (PET/CT) scanning. Radiation treatment planning (RTP) based on $^{68}$Ga-PSMA PET/CT scanning can also lead to some decision modifications. The specific goal of this comparative study is to show how $^{68}$Ga-PSMA PET/CT images can influence the target volume delineation (TVD) and normal tissue radiation dose for PCa RTP, and to compare gross tumor volumes (GTVs) delineated using various strategies for $^{68}$Ga-PSMA PET-based image segmentation techniques.

**Methods**: This study consisted of eleven $^{68}$Ga-PSMA PET/CT images related to patients affected with locally advanced PCa. Four strategies also included manual segmentation techniques, a 2.5 standardized uptake value (SUV) cutoff (SUV=2.5), as well as a fixed threshold of 40% and 50% of the maximum signal intensity (SUV=%40 $SUV_{max}$ and SUV=%50 $SUV_{max}$) for $^{68}$Ga-PSMA PET-based segmentation techniques to delineate $GTV_{PET}$. Two treatment planning were accordingly generated for each patient based on manual $GTV_{PET}$ and CT-only.

**Results:** The GTV was statistically and significantly smaller for PET/CT-derived volumes (9.39 vs. 77.98 $cm^3$ for CT alone) ($p<0.002$). There was no significant difference in volumes of $GTV_{2.5}$ and $GTV_{40\%}$ with $GTV_{man}$ ($p=0.11$) although we observed a significant difference in volumes of $GTV_{50\%}$ with $GTV_{man}$ ($p=0.02$). Mean bladder dose (MBD), V50 of rectum, and mean femoral dose (MFD) for PET/CT plans were significantly lower than CT-only (22.36 vs. 46.55 Gy; $p=0.004$), (33% vs. 67.82%; $p=0.000$), and (28.01 vs. 37.12Gy; $p=0.013$); respectively.

**Conclusion:** The contribution of hybrid modalities of PSMA-PET/CT can be useful for detailed target volume planning and reduce radiation exposure to organs at risk. Using molecular images in RTP also demonstrates the biological volume of GTV so that it will not be left out of the field to cause recurrent tumor.

**Key words:** $^{68}$Ga-PSMA PET/CT Scanning; Prostate cancer; Image segmentation; Radiation treatment planning

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## INTRODUCTION

Gallium-68-labelled prostate specific membrane antigen ($^{68}$Ga-PSMA) is known as a radiotracer with higher sensitivity to detect the presence of pelvic, prostate, and extra-pelvic metastasis. The use of the $^{68}$Ga-PSMA with positron emission tomography/computed tomography (PET/CT) scanning technique has opened up one of the most promising ways to make an accurate diagnosis and staging at the same time it once compared with PET/CT imaging [1, 3]. Toloza et al. published pooled analyses of sensitivity and specificity for PET/CT scanning in comparison with pathologic staging of disease presenting in the mediastinum and found that the pooled sensitivities and specificities for CT had been %57 and %82; respectively. Moreover, the pooled specificities and sensitivities for PET/CT scanning had been %89 and %84 [4]; respectively. The important role of PET and CT imaging in radiation treatment planning (RTP) has been also outlined by the International Atomic Energy Agency (IAEA) [5].

It is widely accepted that $^{68}$Ga-PSMA PET/CT imaging possibly improves the success rate of prostate radiotherapy (RT) via modification of target volume delineation (TVD) and dosage for sufficient coverage of local diseases [6-8]. In another study the effect of $^{68}$Ga-PSMA PET/CT imaging for lymph node detection has proved as well [9].

Hence, Radiation Therapy Oncology Group (RTOG) 0515 [10] has been developed for quantifying the impacts of PET/CT scanning in comparison with CT alone on quality of RTPs. As stated in numerous research studies, PET/CT imaging affects the size of the target volume of radiation treatment (RT). Bradley et al. also illustrated the use of the above-mentioned research by reviewing publications [11]. Many studies accordingly combined further data obtained by PET via side-by-side comparisons of CT and PET images or digital overlay of PET and CT information (i.e. image fusion) [12-14].

For example, Nestle et al. performed a retrospective research by incorporating PET outputs and found that the shape and the form of radiation portals had changed in 12 of 34 patients (35%) [15]. In addition, Munley et al. conducted a retrospective research on lung cancer patients, undergoing pre-irradiation SPECT lung perfusion scintigraphy (n=104) and 18F-fluorodeoxyglucose (FDG) PET (n=35) beside the standard CT scanning of the thorax applied for performing RTP [16] and revealed that, among 35 patients, 12 (34%) had shown a portion of the beam aperture expanded beyond the early designs based on CT itself. However, for many cases, CT-defined target volume had been enveloped by PET-defined target volume. Therefore, the therapy planner had become convinced that differences between target volumes had not stemmed from co-registration errors. PET imaging data also did not change beam orientation on the basis of the CT-defined objective. In addition, Mac Manus et al. in a prospective trial had applied diagnostic PET examinations for RTP [17]. Among 102 patients who had experienced definitive irradiation, PET had significantly increased in target volumes in 22 cases due to incorporating structures formerly regarded but not included by tumor. Moreover, target volume had considerably decreased among 16 patients because PET had revealed the lung consolidation zones or expanded lymph nodes with lower FDG uptakes neglected in treatment volumes. Furthermore, primary tumors had been observed on PET in three patients, which had not been identified on CT. Table 1 reports impacts of PET/CT contribution to RTs.

The precision of GTV definition would be necessary in conformal radiation treatments (CRTs). Earlier studies have indicated that $^{68}$Ga-PSMA PET/CT scanning has the benefit of capacity for providing more accurate definition of GTV and reducing inter-observer variability [18]. Recent threshold-based strategies are also known as automatic techniques with a widespread usage for PET target delineations in various studies and clinical utilizations.

**Table 1:** Impact of FDG-PET on radiation treatment planning (RTP).

| Authors | Number of patients | Fusion method | Impact on RTP |
|---|---|---|---|
| Nestle et al. | 34 | Visual | 35% |
| Munley et al. | 35 | Visual | 34% |
| Brianzoni et al. | 24 | Hardware | 50% |
| Giraud et al. | 11 | Software | 45% |
| Erdi et al. | 11 | Software | 100% |
| Bradley et al. | 26 | Software | 58% |

Even though further methods are available with low success rates including region growing [19] as well as statistical model-based [20], gradient-based [21], and PET/CT-based [22] methods, additional clinical validations are required. It is notable that the present report investigated which fixed or absolute value thresholds were appropriate for $^{68}$Ga-PSMA as the newest specific radiotracer for prostate cancer (PCa) compared with manual contour as the gold standard method.

In the current study, the location of $^{68}$Ga-PSMA PET/CT lesion was mapped, the impact of $^{68}$Ga-PSMA PET/CT imagining on TVD for PCa RT was evaluated, the normal tissue radiation dose was measured, and finally various strategies for GTVs delineated based on $^{68}$Ga-PSMA PET images were compared. Furthermore, it was hypothesized that the $^{68}$Ga-PSMA PET/CT scanning would provide a biological target altering CRT planning.

## METHODS

### Patients

$^{68}$Ga-PSMA PET/CT images were retrospectively used from 11 patients who had not undergone prostatectomy but had been diagnosed to have PCa (median prostate-specific antigen (PSA): 3.51 ng/ml, range: 0.87-89.60) and they were candidate for radiation therapy. In all the images, patients had been positioned supine with arms overhead and scanned by a Siemens PET/CT scanner.

### Validating PET/CT image fusion

The image fusion of CT-only datasets and PET images were checked by the 3DSlicer (version 4.8.1) software in order to control the accuracy. In this way, PET images were registered to CT ones in the 3DSlicer software. Moreover, three markers were used on the fused image. Then, the Hounsfield unit (for CT image) and the activity count (for PET image) of those points were changed in order to be visible in the treatment planning system (TPS). Both images were also imported into the TPS. Finally, they were manually registered using the three points.

### Gross tumor volume (GTV) delineation

It is notable that $^{68}$Ga-PSMA PET/CT images were interpreted by a team including a qualified nuclear medicine physician, a radiation oncologist, and a skillful medical physicist. The images were also reviewed and interpreted by a multi-modality computer platform (Syngo Multi-Modality Workplace; Siemens Medical Solutions: Germany). Then, the region of the enhanced $^{68}$Ga- PSMA uptake that had been more intense compared with the tissues around was defined as the malignant, which could be related to PCa. It is subjective to employ the standard uptake values (SUVs) to determine malignant engagement or to delineate tumor targets. All PET studies have also shown at least one site of abnormal $^{68}$Ga-PSMA uptake. Moreover, maximum SUV ($SUV_{max}$) was computed for the regions of interest (ROIs). In addition, clinical target volumes (CTVs) including the prostate and critical organs surrounding the target such as the rectum, bladder, and femurs were contoured on the CT portion of PET/CT scanning according to the RTOG protocol 0126 [23] by a radiation oncologist blinded to the PET outputs. Then, one of the nuclear medicine physicians analyzed and examined the $^{68}$Ga-PSMA PET/CT images.

Four image segmentation procedures were applied for delineation of the $^{68}$Ga-PSMA PET GTVs. Then, a comparison was made between the outputs and the manual PET contour GTV (i.e. $GTV_{man}$) as the existing gold standard segmentation [24]. PET image segmentation techniques included manual delineation of contours ($GTV_{man}$) by a nuclear medicine physician, a 2.5 SUV cutoff ($GTV_{2.5}$), as well as a fixed threshold of 40% and 50% of the maximum signal intensity ($GTV_{40\%}$ and $GTV_{50\%}$).

### Radiation treatment planning

The CT images were obtained with 3 mm slice thickness. For the CT dataset contour and planning, the volume encompassed the tumor plus 10 mm in each direction except the posterior. To spare the rectum, 6 mm margin was added to the CTV in a posterior direction. For the PET dataset, the same contours were also used for normal tissues surrounding the target (bladder, rectum, and femurs) obtained from the CT dataset, but the primary tumor volume on the PET scan that exceeded 15 mm in each diameter (according to RTOG 0515) except for the posterior was employed to identify the PET planning target volume ($PTV_{PET}$). It should be noted that 10 mm margin was added to spare the rectum more in a posterior direction. The impacts of the PET/CT fusion were then determined for all patients through a comparison between gross tumor volumes (GTVs) obtained from the two separate datasets and the optimal 3D CRT planning via two individual datasets (PET/CT & CT-alone) established by measures of normal tissue toxicity (MBD, rectum V50, and mean femoral dose (MFD)). The dose constraints were considered according to Table 2. Two treatment plans were additionally made for all patients. One plan based on manual $GTV_{PET}$ (as the gold standard segmentation in molecular images) and the other applied the CT-only (as the routine segmentation technique).

**Table 2:** Dose constraints for OAR; QUANTEC recommendations.

| Critical structure | Dose-volume parameter |
|---|---|
| Bladder | Mean dose<65 Gy |
| Rectum | V50<60 Gy † |
| Femoral heads | Mean dose<52 Gy |

† 50% of the rectum volume should be received <60 Gy

It was found that it was not important to specify the prescribed dose, compensation filters, wedges, beam energy, and so forth. However, one specific requirement needed to be implemented i.e. the above-mentioned factors should be similar for the two CT-only and PET/CT datasets for all patients. Moreover, each plan was optimized for high compatibility of the described enclosing isodose (95% isodose). In addition, prescription of total dosage of 70 Gy was performed for the reference point.

### Statistical analysis of GTVs

Based on the research plan, the IBM SPSS Statistics (version 22) (Chicago; IL: USA) was used to do the statistical analyses. The distribution of the differences was also fulfilled to assess the outputs. A one-sided one-sample paired t-test was further employed for the difference in the case of the normal distribution of the differences. Apart from that, non-parametric Wilcoxon matched-pair signed-rank test was utilized with the overall level of significance of 0.05.

## RESULTS

The present study made a comparison between two RTP techniques via PET/CT fusion and CT alone. Moreover, the impact of the PET/CT fusion was shown separately for all patients through a comparison of GTV contours on each modality (PET and CT). Table 3 compares the measured lesion volumes obtained from CT and PET imaging. In addition, mean GTV for PET ($GTV_{man}$) was 9.39 $cm^3$ vs. 77.98 $cm^3$ for CT-only ($p<0.002$). Figure 1 represents the instance of the reduced GTV through the PET-defined tumor volumes. As well, Figure 2 shows a part of the $GTV_{man}$ for the PET/CT-extracted target volumes with high SUV out of the target volume obtained from CT-only.

It should be mentioned that the contours specified by the means of the $GTV_{2.5}$ could not offer substantial delineation in five cases (45% of the patients) according to the manual lesion volume contour. In addition, considering the $GTV_{\%40}$ or $GTV_{\%50}$ for the definition of the GTVs, PET-based techniques failed in 6 cases (54% of the patients) (Table 4).

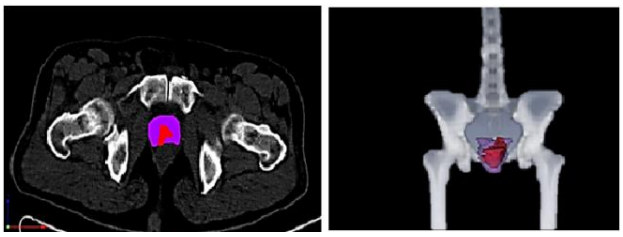


**Fig 1.** Mapped volumes ($Cm^3$) of $^{68}$Ga-PSMA (red) and CT (purple) Shows the difference in volume.

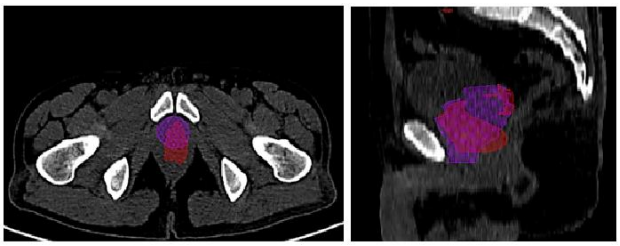


**Fig 2.** Mapped location of $^{68}$Ga-PSMA (red) and CT (purple) shows the difference in place.

Figure 3 portrays the comparison between the median GTVs based on PET datasets with CT-only. Overall, all the GTVs described on the PET-based methods were commonly smaller compared with the CT defined (Table 5). However, the resultant $GTV_{2.5}$ for the PET/CT-extracted target volumes would not achieve statistical significance with the $GTV_{man}$ ($p=0.11$; Wilcoxon matched-pair signed-rank test). Moreover, no significant differences were found in the target volume $GTV_{\%40}$ with $GTV_{man}$ derived by PET/CT scanning ($p=0.11$; Wilcoxon matched-pair signed-rank test). However, there was a slight difference in the target volume $GTV_{50\%}$ with $GTV_{man}$ ($p= 0.02$; Wilcoxon matched-pair signed-rank test). Figure 4 displayed the target volume definition in four strategies. So this study suggest the manual segmentation method for all the patients after the use of the other methods to recheck.

### Dosimetric analysis

For eleven prostate cancer patients, 3D CRT plans were implemented for two distinct datasets (i.e. PET/CT & CT-only). Figure 5 shows the dose received by each patient. In addition, the impacts of the PET/CT fusion on treatment planning were measured by MBD, V50 of rectum, and MFD. According to the research plan, the MBD, V50 of rectum, and the MFD in all the patients with PCa through the CT scans were 46 Gy (i.e. the estimated standard deviation (SD) 0.14 Gy), 47 (that is, the estimated SD 0.13), and 37 Gy (viz. the estimated SD 0.03 Gy).

**Table 3:** Differences in volumes between CT-only and manual PET contour.

| Variable | GTV Volume (cm3) | | | |
|---|---|---|---|---|
| | CT-only | Manual PET | Difference (PET-CT only) | P-value† |
| Patient NO. 1 | 63.59 | 20.24 | -43.35 | |
| Patient NO. 2 | 32.08 | 2.80 | -29.28 | |
| Patient NO. 3 | 37.82 | 17.01 | -20.81 | |
| Patient NO. 4 | 129.45 | 31.25 | -98.20 | |
| Patient NO. 5 | 215.85 | 6.54 | -209.31 | |
| Patient NO. 6 | 64.38 | 9.41 | -54.97 | 0.002 |
| Patient NO. 7 | 50.09 | 2.81 | -47.28 | |
| Patient NO. 8 | 78.83 | 0.82 | -78.01 | |
| Patient NO. 9 | 107.56 | 4.46 | -103.10 | |
| Patient NO. 10 | 48.16 | 6.86 | -41.30 | |
| Patient NO. 11 | 30.01 | 1.19 | -28.82 | |

† Independent t-test

**Table 4:** Quantities and percentage of SUV in manual PET contour for each patient.

| Patient No. | Manual PET contour | |
|---|---|---|
| | SUV | %$SUV_{max}$ |
| 1 | 3 | 10% |
| 2 | 5.4 | 23% |
| 3 | 2.22 | 7% |
| 4 | 3 | 18% |
| 5 | 3 | 50% |
| 6 | 2.86 | 40% |
| 7 | 3.04 | 65% |
| 8 | 2.65 | 57% |
| 9 | 2.73 | 23% |
| 10 | 2.74 | 9% |
| 11 | 2.4 | 39% |

P-value=0.074 ($SUV_{man}$ vs. SUV=2.5); P-value=0.17 (%$SUV_{man}$ vs. 40%); P-value=0.011 (%$SUV_{man}$ vs. 50%)
One-sided one-sample t-test

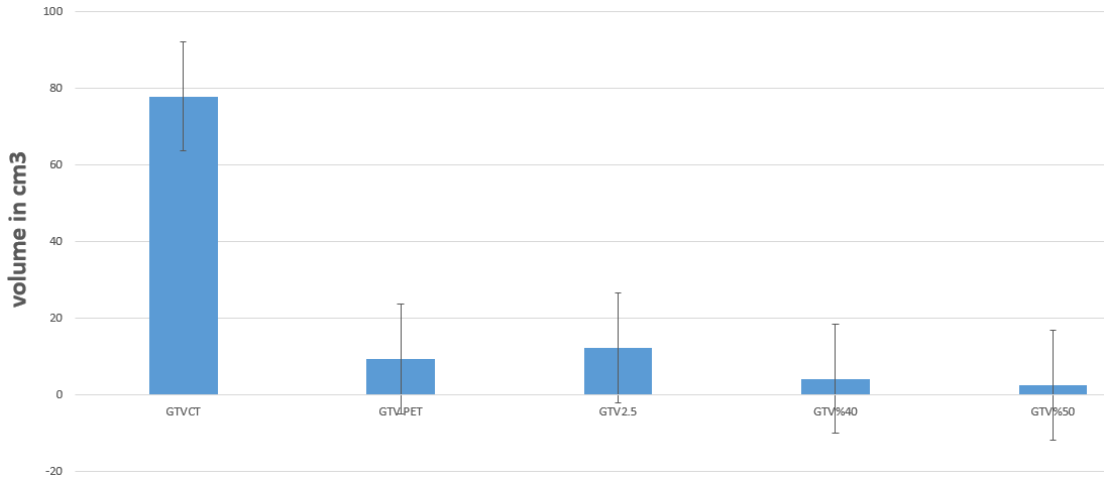



**Fig 3.** Gross tumor volumes (GTV, $cm^3$) in four PET-based-GTV delineation techniques.

**Table 5:** Differences in volumes between manual PET contour and typical thresholds ($cm^3$).

| Patient No. | Manual PET contour ($GTV_{man}$) | SUV=2.5 ($GTV_{2.5}$) | %40 $SUV_{max}$ ($GTV_{\%40}$) | %50 $SUV_{max}$ ($GTV_{\%50}$) |
|---|---|---|---|---|
| 1 | 20.24 | 22.84 | 13.53 | 2.64 |
| 2 | 2.8 | 5.10 | 0.95 | 0.63 |
| 3 | 17.01 | 15.71 | 12.23 | 11.29 |
| 4 | 31.25 | 36.94 | 18.56 | 3.82 |
| 5 | 6.54 | 9.90 | 10.66 | 6.54 |
| 6 | 9.41 | 4.06 | 11.88 | 1.62 |
| 7 | 2.81 | 5.75 | 13.04 | 7.94 |
| 8 | 0.82 | 1.45 | 1.54 | 1.04 |
| 9 | 4.46 | 4.91 | 2.16 | 1.57 |
| 10 | 6.86 | 7.37 | 5.07 | 0.62 |
| 11 | 1.19 | 1.11 | 1.09 | 0.59 |

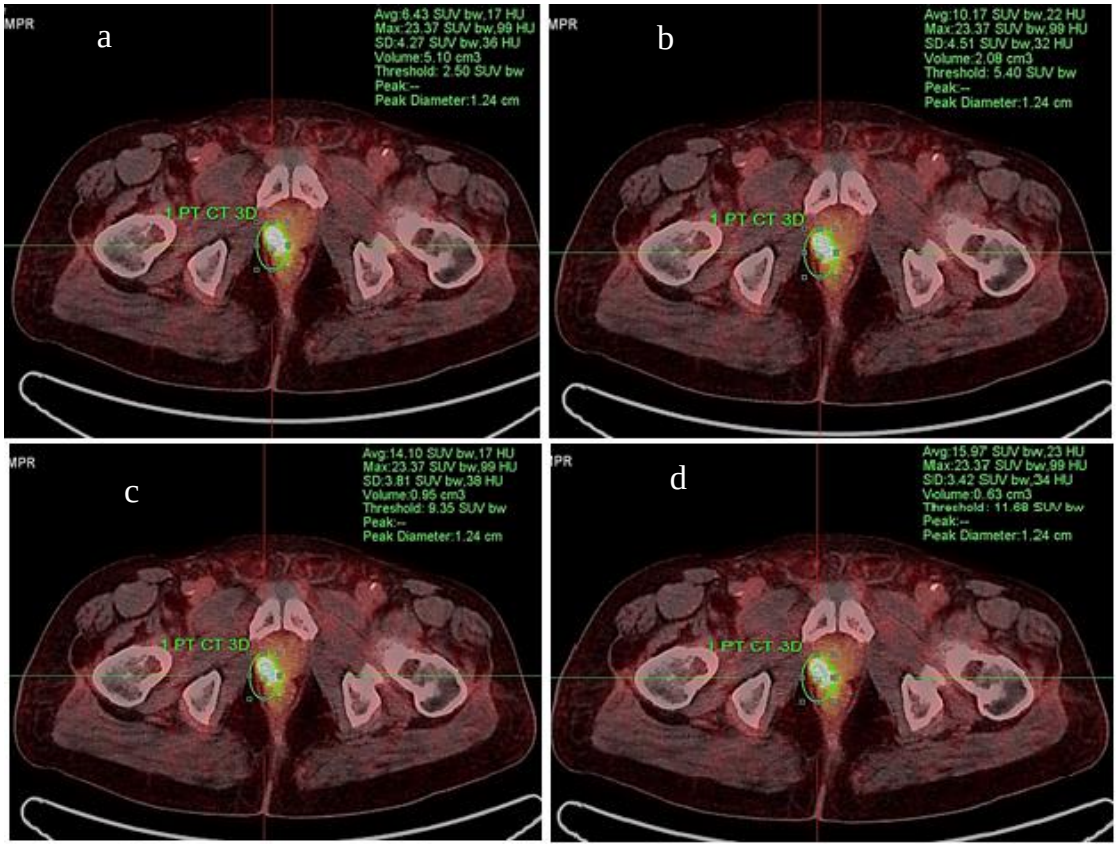
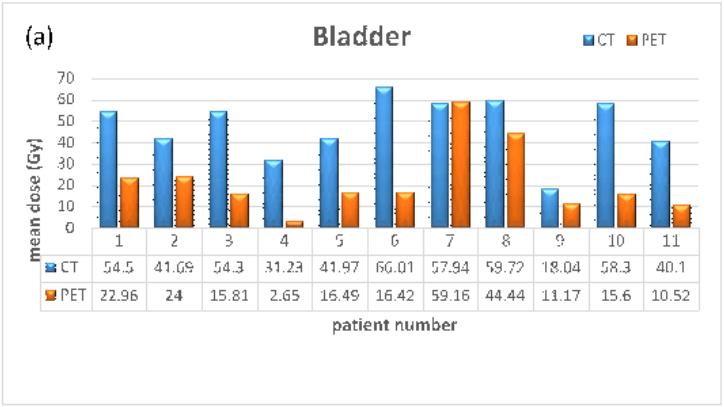
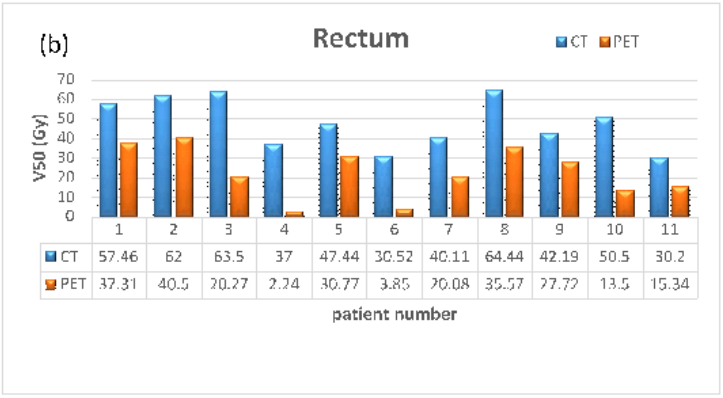



**Fig 4.** Representative PET/CT image in four PET-based-GTV delineation techniques. (a): SUV=2.5, (b): manual technique, (c):SUV=%40 SUVmax, (d): SUV=%50 SUVmax.

Likewise, using the PET datasets, the MBD, V50 of rectum, and the MFD were 22 Gy (i.e. the estimated SD 0.17 Gy), 23 (that is, the estimated SD 0.13), and 28 Gy (viz. the estimated SD 0.08 Gy). According to the predictions, smaller volume of the tumor significantly caused lower MBD (22.36 vs. 46.55 Gy; p=0.004), V50 of rectum (23.36 vs. 47.48; p= 0.000), and MFD (28.01 vs. 37.12Gy; p= 0.013) (Table 6). The difference column shows the percentage of difference between the two means. It should be noted that one-sided one-sample paired t-test was employed for analysis.



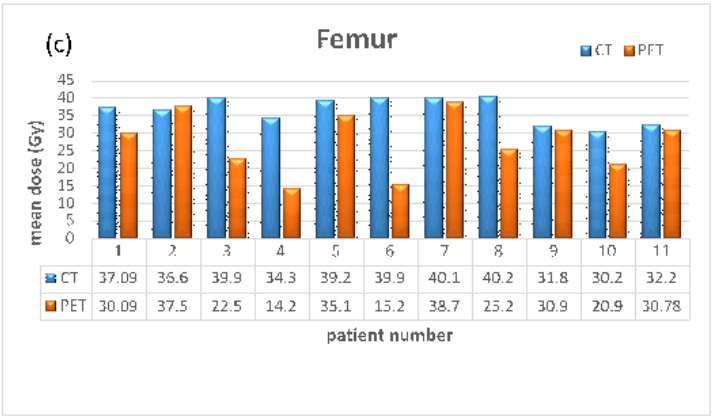




**Fig 5.** Dose value differences to OARs: (a) bladder, (b) rectum, (c) femur between the two techniques

**Table 6:** Comparison of organs at risk dose in two treatment planning techniques

| Organ | CT-only | | PET/CT | | Difference (%) |
|---|---|---|---|---|---|
| | Mean (cGy) | SD | Mean (cGy) | SD | |
| Bladder | 4655 | 14.4 | 2236 | 17 | 108.1 |
| Rectum | 4748 | 13.4 | 2336 | 13 | 103.2 |
| Femoral heads | 3712 | 3.3 | 2801 | 8.6 | 32.5 |

## DISCUSSION

This study was to determine the best SUV threshold for the newest radiotracer i.e. the $^{68}$Ga-PSMA, used for PCa treatment. Therefore, two treatment plans were compared based on the $^{68}$Ga-PSMA PET/CT tumor volume delineation datasets and the CT-only.

According to the results of this study, all the GTVs describing the PET-based segmentations ($GTV_{PET}$ as the gross tumor volume defined by the PET) were usually smaller compared with the CT defined ($GTV_{CT}$; gross tumor volume defined by CT only) (Table 5). Many studies had also indicated the same results [25-27]. As mentioned in the IAEA consensus 2014, the TVDs based on the PET/CT are on the average smaller than the CT-only based technique. Moreover, it causes dose reduction to normal structures [28]. In a case that the PET volumes may be delineated precisely, it may raise the possibility of dose escalation and dose painting to the target so it can further cause sub-optimal tumor controls by increasing dose to the sub volumes inside the tumor which have resistance to radiation [29] in order to prevent the recurrence.

Some other quantitative or semi-quantitative contouring methods based on the SUV were also implemented. In some studies, the authors declared that the fixed threshold (SUV=2.5) was appropriate for lesion detection by the PET/CT modality [30-32] which were consistent with the results of the present study ($GTV_{2.5}$ vs. $GTV_{man}$ p =0.11; Wilcoxon matched-pair signed-rank test). Moreover, comparison of the $SUV_{man}$ (the value of SUV in the PET manual contour) with SUV=2.5 confirmed the results ($SUV_{man}$ vs. SUV=2.5 p=0.074; one-sided one-sample t-test). Accordingly, the use of the fixed percentage of the SUV (SUV≥ %40 $SUV_{max}$) showed a good conformity with the lesion volume determined manually (GTV %40 vs. $GTV_{man}$ p=0.11; Wilcoxon matched-pair signed-rank test). The results were also in good agreement with the findings reported in some other studies [31, 33, 34]. Nevertheless, it was found that the other fixed percentage of the SUV (SUV≥%50 $SUV_{max}$), used in this study, was not appropriate (GTV%50 vs. $GTV_{man}$ p= 0.02; Wilcoxon matched-pair signed-rank test). In this respect, Nestle et al. quantitatively presented a comprehensive review of several parameters and shortcomings for tumor volume delineation for RT [15]. In both retrospective studies, authors declared that they observed a decrease in target volume and field size in all patients by using PET images in treatment planning although they studied on lung cancer.

The present study confirmed the results reported by recent investigations so that the $^{68}$Ga-PSMA PET/CT would be taken into account as a worthwhile diagnostic tool to modify RTP [35, 36].

All the normal tissue structures (e.g. bladder, rectum, and femurs) had been influenced by the difference in GTV, which had received a much lower dosage in comparison with their tolerated dose in PET/CT planning. As mentioned in some other studies [37-40], the PTV reduction based on the smaller $GTV_{PET}$ could spare the normal-tissue more effectively.

According to these results, all the patients had planning modification (%100 impact); therefore, $^{68}$Ga-PSMA PET/CT, as a specific radiotracer for PCa, could possibly improve the success rate of the prostate RT via changes in the target volume delineation and dosage for adequate coverage of local diseases. It would be also regarded as a promising tool for individualized salvage therapy planning.

This retrospective study faced a major limitation in terms of lack of lesion validation. Hence, it could not surely eliminate the probable $^{68}$Ga-PSMA false-positive outputs. However, the nuclear medicine physician as the interpreter was cautious to avoid certain drawbacks and to examine CT as well as $^{68}$Ga-PSMA PET images. In addition, the research considered possible impacts of the $^{68}$Ga-PSMA PET/CT on RTP based on traditional treatments, which hardly contained molecular extension.

## CONCLUSION

This retrospective study aimed to treat a cohort of the 11 cases suffering from the localized PCa indicated the possibly significant impact of $^{68}$Ga-PSMA-11 PET/CT on the ultimate RTP. PSMA-positive lesion which is not entailed by the planning volumes on the basis of the CTVs (derived by the CT-only dataset) regarded as an essential possible effect on therapy planning, so remarkable improvement occurs by the aid of PET/CT demonstrating the impacts of using molecular imaging for GTV definition, but choosing a segmentation method for the target volume definitions of PCa according to the PET imaging could be significant. It should be noted that absolute PET volumes depended on the segmentation technique employed. Moreover, delineating through $SUV_{2.5}$ and $SUV_{\%40}$ $SUV_{max}$ were relatively preferred. Furthermore, it would not be dependent on the observer difference. In general, the PET volumes were smaller in comparison with those of CT; however, PET could identify the probable tumor regions not identified via the traditional CT-based technique. This might possibly enhance the accuracy of the GTV definition. Further prospective and histologic validation research studies are thus needed prior to the routine use of $^{68}$Ga-PSMA PET data for optimizing the CT-extracted target volume.

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