Evaluation of Dose-Painting in the Dominant Intraprostatic Lesions by Radiobiological Parameters using ^{68}Ga-PSMA PET/CT

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ABSTRACT

Background: Patients diagnosed with dominant intraprostatic lesions (DIL) may need radiation doses over than 80 Gy. Dose-painting by contours (DPC) is a useful technique which helps the patients. Dose-painting approach need to be evaluated.

Objective: To evaluate the DCP technique in the case of boosting the DILs by radiobiological parameters, tumor control probability (TCP), and normal tissue complication probability (NTCP) via PET/CT images traced by ^{68}Ga-PSMA.

Material and Methods: In this analytical study, ^{68}Ga-PSMA PET/CT images were obtained from patients with DILs that were delineated using the Fuzzy c-mean (FCM) algorithm and thresholding methods. The protocol of therapy included two phases; at the first phase (ph1), a total dose of 72 Gy in 36 fractions were delivered to the planning target volume (PTV1); the seconds phase consisted of the application of variable doses to the PTV2. Moreover, two concepts were also considered to calculate the TCP using the Zaider-Minerbo model.

Results: The lowest volume in DILs belonged to the DIL1 extracted by the FCM method. According to dose-volume parameters of the rectum and bladder, by the increase in the PTV dose higher than 92 Gy, the amounts of rectum and bladder doses are increased. There was no difference between the TCPs of DILs at doses higher than 86 Gy and 100 Gy for ordinary and high clone density, respectively.

Conclusion: Consequently, our dose-painting approach for DILs, extracted by the FCM method via PET/CT images, can reduce the total dose for prostate radiation with 100% tumor control and less normal tissue complications.

Introduction

Prostate cancer is known as a multifocal disease [1]. Several lines of evidence identified that prostate carcinoma is disseminated via clones from such Dominant Intraprostatic Lesions (DILs). A single or few DILs consists of a large majority of tumors that typically accounts for less than 10% of the total gland volume. Importantly, DIL is the most common site of recurrence after radiation therapy [2]. Detection and classification of DILs play a significant role in the diagnosis and assessment of radiotherapy response in patients with prostate cancer

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(PCa) [3].

Patients diagnosed with DIL may need radiation doses over than 80 Gy based on the method of Intensity-modulated radiotherapy (IMRT). Delivering high doses of radiation to prostate-only fields via radiation therapy may influence the adjacent tissue structure of the prostate and increase the complication of therapy. Dose-painting by contours (DPC) is a useful technique, helping deliver precise radiation doses to tumor sub-volumes by targeting DILs, which are defined by molecular or functional imaging [4]. DPC technique requires a precise localization of DILs. ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) is a new functional imaging method applied for imaging prostate cancer characterized by the increased expression of prostate-specific membrane antigen (PSMA, glutamate carboxypeptidase II, EC3.4.17.21).

A large number of segmentation techniques have been developed for the extraction of DILs by PET images. In this context, thresholding techniques have been proposed to overcome difficulties in operator-based methods to detect DILs. The only parameter that needs to be set in a thresholding technique is the intensity value (threshold) to differentiate the foreground (tumor) from the background [5]. The threshold is expressed as the percentage (e.g., 40%) of the maximum local uptake [6]. The Fuzzy c-mean (FCM) algorithm is another image segmentation method to segment and extract DILs by images of prostate cancer via the PET/CT method. The determination of the precise volume of DILs and delivering an appropriate dose to tumor volume can increase treatment efficiency and reduce tumor recurrence [7].

In this study, we investigated the volume effect of DILs, which was extracted using the threshold method or FCM algorithm to specify the amount of additional prescription dose using the DPC technique. We hypothesized that our proposed dose-painting approach might achieve greater control of DILs and reduce

the side effects of organs at risk located at the proximity of the prostate. Moreover, we applied the RADBIOMOD software version v0.3b to assess the NTCP and TCP.

Material and Methods

Study Design

In this analytical study, we used the images pertaining to patients with localized high-risk prostate carcinoma for initial radiotherapy who underwent ^{68}Ga-PSMA PET/CT functional imaging. The protocols of ^{68}Ga- PSMA PET/CT imaging were performed based on the study by Zamboglou et al, [8]. ^{68}Ga- PSMA PET/CT scans were performed with the PET/CT Biograph 6 True point (Siemens Healthineers, Forchheim, Germany). The scanner was calibrated to ensure the compatibility of the quantitative measurements.

Segmenting and contouring

Two modes of the FCM and thresholding methods were applied to delineate DILs. The thresholding technique included a fixed threshold of 30% and 20% of the maximum signal intensity according to the absorption rate of ^{68}Ga- PSMA in PET images (wang 2009).

The masks were extracted from the PET images and copied to the CT images using the MIM software (MIMSoftware Inc., Cleveland, OH, USA), containing tools for multimodality image fusion, automatic deformable contouring, quantitative functional analysis, diagnostic tools, and remote DICOM [9]. MIM was employed for copying the masks of DILs and converting the structure of the CT images into the RT structure, by which the contouring process is prepared for TiGRT Treatment Planning System (Linatech, Sunnyvale, CA, USA). The CTV1 includes prostate and seminal vesicles. The planning target volume (PTV1) was generated by the addition of a 9-mm margin to the CTV1. DILs, as the boosting sub-volume, are considered the gross tumor volume (GTV). A 5-mm margin was also added to

create the planning target volume (PTV2) for DILs which was far from the rectum or bladder while the addition of a 3-mm margin to DILs, which were adjacent to rectum, did not overlap with the rectum, bladder, and urethra. Furthermore, the organs at risk present in the pelvis region were contoured as follows: the bladder, rectum, and femur neck. The extraction of DILs was carried out by the FCM that was designated as DIL1, and threshold methods, with the threshold of 30% and 20% for DIL2 and DIL3, respectively.

Treatment planning

A two-phase therapy was conducted for each patient. At the first phase (ph1), a total radiation dose of 72 Gy in 36 fractions delivered to the PTV1. At the second phase, different doses of radiation, including 10, 14, 20, 24, 28, 32, and 36 Gy were delivered to the PTV2. Thus, the total delivery dose to DILs was escalated up to 82, 86, 92, 96, 100, 104, and 108 Gy in variable fractions. For all patients, the radiation doses for the DIL1, DIL2, and DIL3 increased for the rectum and bladder to each the acceptable toxicity levels. Seven beams and inverse planning for intensity-modulated radiotherapy were used for both phases. Optimization goals of setting up were adjusted for the 84-Gy arm in the CHHIP trial. Dose-volume histograms (DVHs) for each of the two phases were plotted by the inverse-treatment-planning software to specify the dose distribution. Two DVHs (Ph1 and Ph2) were integrated to gain total DVH. The results of the dose distribution were used to calculate the NTCP (Lyman-Kutcher-Burman model) and TCP (Zaider-Minerbo model) [10] to determine the number of additional fractions needed to optimize radiotherapy with minimum damage to the organs at risk in the pelvis.

Evaluation of Radiobiological treatment plan

RADBIOMOD is a simple program, utilized for biological modeling in radiotherapy plan evaluation. Two concepts are considered to calculate the TCP employing the Zaider-Minerbo model. There is high clone density in DIL(S) and an ordinary clone density in DIL(S) and field. The radiobiological parameters used to calculate the TCP included $\alpha = 0.26$, $\beta = 0.0312$, $\lambda = 0.0165$, clonogenic cell density $= 10^6$ CC^{-1} (for ordinary clone density), and clonogenic cell density $= 10^9$ (for high clone density) CC^{-1}. To calculate the NTCP parameters, the following values $\alpha/\beta = 3$, n = 0.09, m = 0.13, and TD50 = 76.9 for the rectum and $\alpha/\beta = 3$, n = 0.5, m = 0.11, and TD50 = 80 for the bladder were applied [10].

Statistical analysis

The statistical analysis was performed by the SPSS software version 16. The difference between groups was analyzed by the Wilcoxon test. The error bars represent the standard deviations in different experiments. The level of statistical significance was set at p-value <0.05.

Results

Treatment Planning and Modeling

In the present study, 14 patients with at least one DIL in prostate imaging were identified. The size, number of DILs, and the mean volumes of each of the DIL1, DIL2, and DIL3, which were extracted by three different segmentation methods, as shown in Table 1. Accordingly, the differences between each of the above DILs were statistically significant (p=0.005). The smallest volume in DILs mentioned earlier pertained to the DIL1, extracted by the FCM method.

The mean dose delivered to the prostate (PTV1) was 74 Gy, whereas the dose used for the PTV2 increased up to 108 Gy in the second phase. DILs that were close to either the rectum or bladder increased the risk of organ damage in the pelvic region. Dose-volume parameters of the rectum and bladder, as a result of the sum of DVHs in two phases, are report-

Table 1: The mean and range of the prostate volume of 14 patients who had at least one dominant intraprostatic lesions (DIL) in the prostate. While the DIL1 was extracted by the Fuzzy method, the DIL2 and DIL3 were extracted by the thresholding method with the maximum absorbance of 30% and 20%, respectively.

	Mean	Range
Prostate Volume(cm³)	57.67	40.00-83.14
DIL1 volume(cm³)	3.69	1.62-7.42
DIL2 volume(cm³)	7.17	5.47-10.70
DIL3 volume(cm³)	17.12	11.2-22.30
Number of DIL(s)	1.00	1.00-2.00

DIL: Dominant intraprostatic lesion

ed in Tables 2 and 3. According to Tables 2 and 3, the amount of doses employed for the rectum and bladder were similar to the conventional treatment plan doses up to 92 Gy; however, the doses applied for the rectum and bladder increased in parallel with the increase in the total dose of PTV.

Figures 1 and 2 show the TCP of DILs with ordinary and high clone density at the first and second phases of therapy, respectively. As shown in Figure 1, there are significant differences between DILs (1, 2, 3) at a dose range between 72 Gy and 86 Gy. Of note, there was no significant difference between the TCPs of DIL1 and DIL2 at the doses of 82 Gy and 86 Gy.

Accordingly, there were no differences be-

**Table 2:** Treatment planning results for the rectum

	Volume of rectum(cm³)							
Ph1+ph2 dose(GY)	72	82	86	92	96	100	104	108
V40(Gy)	46.7±8.9	48.5±9.1	49.8±15.3	51.5±8.1	52.4±10.0	53.0±11.3	55.8±11.9	56.3±10.2
V65(Gy)	8.2±3.6	14.5±1.8	15.5±2.2	17.8±2.6	19.18±2.7	20.4±3.2	21.8±3.3	22.1±3.6
V70(Gy)	1.56±1.4	7.3±2.9	9.04±3.2	9.98±3.6	11.14±4.2	12.2±4.8	13.3±5.0	14.1±5.3
V75(Gy)	0.0	3.8±0.2	5.4±0.2	6.2±0.6	8.2±3.9	8.7±3.8	9.7±4.5	11.0±4.7
V80(Gy)	0.0	1.4±0.3	2.3±0.4	5.7±.04	6.8±0.4	8.3±0.3	9.26±4.5	9.6±0.9
V95(GY)	0.0	0.0	0.0	0.0	0.0	2.1±0.2	4.5±.2	5.5±0.1
V100(Gy)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
V105(Gy)	0.0.	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 3: Treatment planning results for the bladder

	The volume of the bladder(cm³)							
Ph1+ph2 dose(Gy)	72	82	86	92	96	100	104	108
V40(Gy)	26±1.7	27.5±1.6	27.7±1.6	27.6±1.5	27.7±1.5	27.7±1.5	27.8±1.4	28.8±0.4
V65(Gy)	9.9±3.2	9.7±2.1	9.8±2.1	9.9±2.2	10.1±2.1	10.2±2.1	10.3±2.0	10.4±0.0
V70(Gy)	3.9±0.1	4.8±0.3	5.0±0.4	5.2±0.5	5.4±0.5	5.5±0.5	5.6±0.6	5.6±0.6
V75(Gy)	0.1±0.0	1.2±0.5	1.6±0.07	1.6±0.2	1.96±0.2	2.2±0.2	2.23±0.02	2.4±0.9
V80(Gy)	0.0	0.4	0.2	0.6	1.2±0.6	1.3±0.6	1.4±0.1	1.7±0.1
V95(GY)	0.0	0.0	0.0	0.0	0.3	1.26±0.2	2.4±.1	2.8±.1
V100(Gy)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
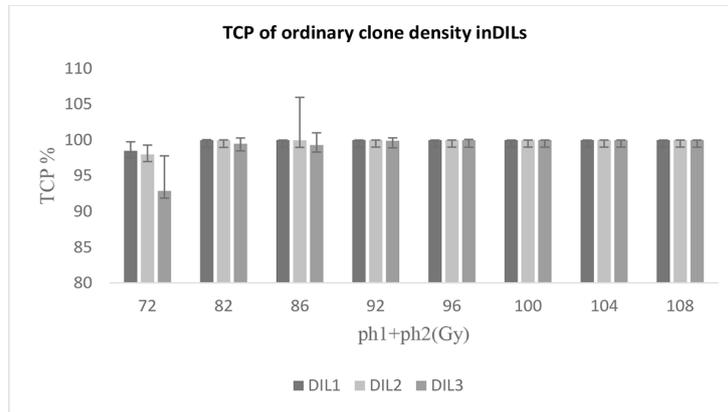
Figure 1: Tumor control probability (TCP) of dominant intraprostatic lesions (DILs) with a dose-painting treatment plan with ordinary clone density DILs (1, 2, 3) at the total dose of 72 Gy at the first phase of the study and the total doses of 82, 86, 92, 96, 100, 104, 108 Gy at the second phase.
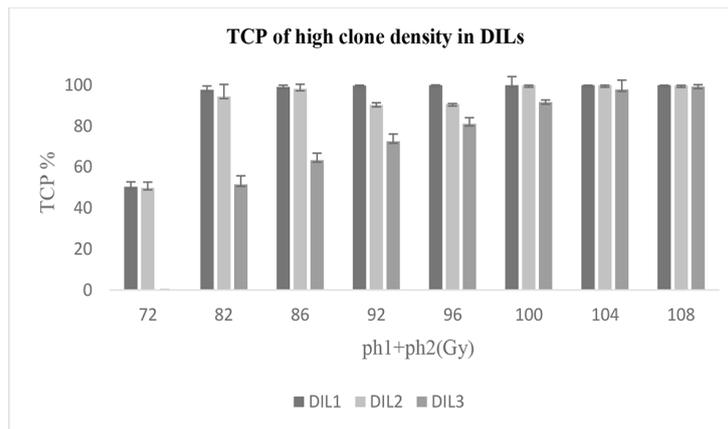
Figure 2: Tumor control probability (TCP) of dominant intraprostatic lesions (DILs) with a dose-painting treatment plan with high clone density DILs (1, 2, 3) at the total dose of 72 Gy at the first phase of the study and the total doses of 82, 86, 92, 96, 100, 104, 108 Gy at the second phase of the treatment plan.

tween the TCPs of DILs at the doses higher than 92 Gy. As shown in Figure 2, in high-density DILs, there were significant differences between the amount of TCPs at the dose range between 72 Gy and 96 Gy, while there was no remarkable difference between the TCPs of DILs at the doses higher than 100 Gy (p<0.05). Apparently, the values of the TCPs reached 100% in all DILs at the doses higher than 100 Gy.

Figures 3 and 4 indicate the amounts of NTCPs belonging to the rectum and bladder, respectively at the dose range of 72 Gy and 108 Gy. For both rectum and bladder, upon the increase in radiation doses up to 100 Gy, the values of NTCP markedly increased. On the other hand, there were no significant differences between the NTCPs when compared at the dose spectrum between 100 and 108 Gy.

Discussion

Multifocality of prostate cancer has been revealed in prostatectomized specimens. Local recurrence after RT is associated with one or more DILs located at the primary tumor locations [11]. There are several imaging tech-
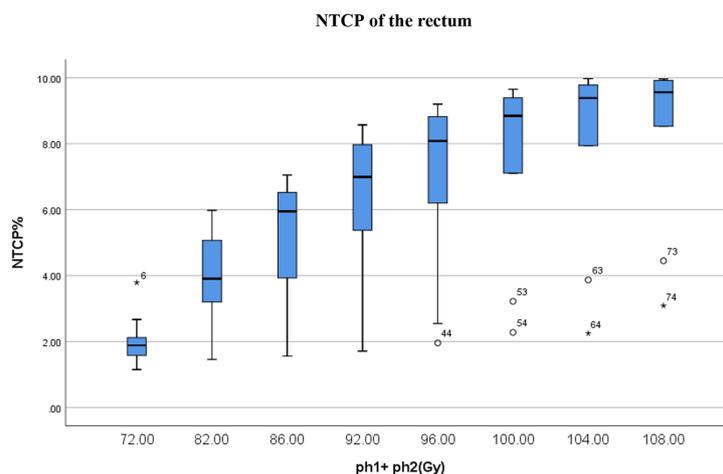
Figure 3: The normal tissue complication probability (NTCP) of the rectum following treatment with 72 Gy at the first phase and the total doses of 82, 86, 92, 96, 100, 104, 108 Gy at the second phase of the treatment plan.
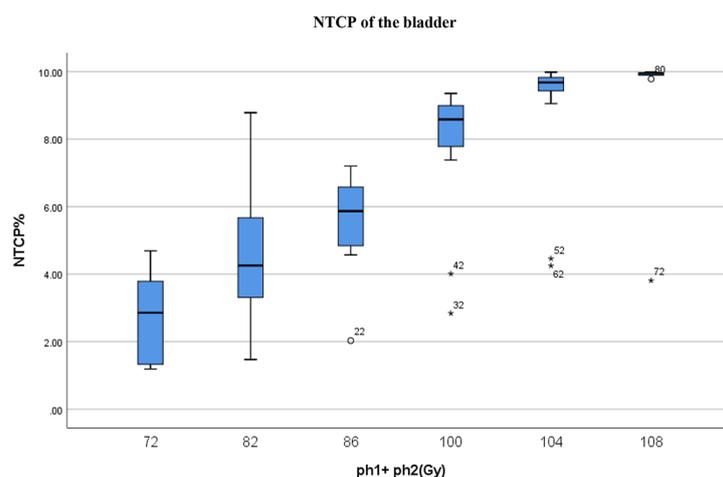
Figure 4: The normal tissue complication probability (NTCP) of the bladder 72 Gy at the first phase and the total doses of 82, 86, 92, 96, 100, 104, 108 Gy at the second phase.

niques for the diagnosis and characterization of DILs [12]. PET/CT is one of the imaging modalities in which ^{68}Ga -PSMA is applied for the determination of DILs in prostate [13]. Improving therapeutic response by boosting DILs and maintaining the standard dose in the rest of the prostate is the aim of external beam radiotherapy treatment. Boosting may increase the total dose in the pelvis region and make complications in the bladder and rectum [14]. Thus, an increment in the TCP without increasing the NTCP in risk organs at risk is an ideal goal in prostate radiotherapy [15] that would be achieved by the dose-painting techniques.

In the current study, DILs were characterized by the PET/CT images using two modes, including the FCM and thresholding methods with a maximum absorbance of 30% and 20% of ^{68}Ga- PSMA. According to our data (Table 1), the DIL1 that was extracted by the Fuzzy method (FCM) had the minimum volume compared with the DIL2 and DIL3, extracted by the thresholding technique, indicat-

ing that FCM is more accurate to estimate the size of sub-volumes in prostate lesions. It is now known that blurring in PET images reduces the spatial resolution (4-5 mm) and contrast, resulting in the exaggerated size of DILs concerning their real size. Therefore, the lack of enough resolutions in images causes some problems to precisely determine the lesion boundaries and estimate the precise size of DILs. Moreover, the FCM technique is capable of determining tumor boundaries in PET scans and defining the volume of DILs more accurately, resulting in boosting the sub-volumes as a result of delivering higher doses and inhibition of the local recurrence following RT [16, 17]. In the current study, we compared the proposed dose-painting approach with the standard RT using the TCPs of DILs (1, 2, 3) (Figures 1 and 2), and for simplicity, we demonstrated one NTCP for the three characterized DILs (DILs 1, 2, 3) (Figures 3 and 4). In our dose-painting approach, we showed that the TCP in all DILs with ordinary clone density was elevated up to 100% at the doses higher than 92 Gy while the NTCP did not exceed 9.3%. Moeover, the TCP reached 100% at the dose of 100 Gy in high clone density DILs.

We can observe the TCPs for the DIL1 in both ordinary and high clone densities that reached 100% at the dose of 82 Gy (Figures 1 and 2). The NTCP for both rectum and bladder increased in a dose-dependent manner; however, it did not exceed 9.3% even at high doses such as 108 Gy (Figures 3 and 4). Other studies indicated that the unlethal doses above 80 Gy increase the risk of strictures [18]; yet, in our study, this dose was limited to 76 Gy. It has been shown that by the precise characterization of DILs in prostate lesions, we can deliver lower doses to achieve 100% tumor control. Thus, our data showed that the FCM method has the potential to extract DILs for delivering the optimum dose with high tumor control and less complication in normal tissues.

In a dose-painting protocol, when high doses of radiation are applied for boosting DILs, target displacement; e.g., the peristaltic motions of the bladder and rectum [19] may damage the organs at risk located at the proximity of the GTV [20, 21]. Thus, in the present study, the PTV was constructed by the addition of a 5-mm margin to DILs to reduce inaccuracies, caused by movement, imaging, or fusion processes. However, in some treatment plans that DILs are adjacent to the rectum and bladder, and a 3-mm margin is added to the PTV to decrease the overlap between the PTV and normal tissues.

Consequently, our dose-painting approach for characterization of DILs, extracted by the FCM method via the PET/CT images, can reduce the total dose of the prostate with 100% tumor control and less normal tissue complication. However, uncertainties and day-to-day anatomical variations confine the applicability of the approach for optimization.

Conclusion

In the current study, the PET/CT scans using the Ga-PSMA tracer was used to determine DILs in prostate cancer. DILs were delineated using the FCM and thresholding methods with the maximum absorbance of 30% and 20% of ^{68}Ga-PSMA. We showed that DILs, extracted by Fuzzy methods, had smaller volume compared with those extracted by the thresholding method. Our proposed dose-painting protocol showed that TCP reached 100% in DILs, extracted by the FCM at the dose of 82 Gy. Moreover, we demonstrated that by escalating the dose up to 108 Gy, the NTCP would not exceed 9.3%. It seems that further studies are needed to evaluate the displacement and position of DILs in the prostate.

Acknowledgment

Conflict of Interest

None

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