Feasibility and safety of definite volumetric modulated arc therapy with simultaneous integrated boost to the dominant intraprostatic lesion in patients with unfavorable intermediate to high-risk prostate cancer

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ABSTRACT

Background: The most common site of recurrence of prostate cancer after definite radiation therapy is the dominant intraprostatic lesion (DIL). This study aimed to investigate the feasibility and safety of definite volumetric modulated arc therapy (VMAT) with simultaneous integrated boost (SIB) to the DIL in patients with unfavorable intermediate to high-risk prostate cancer.

Materials and methods: In this prospective uncontrolled clinical trial, patients were delivered VMAT at a dose of 87.75 Gy in 39 fractions or 70 Gy in 20 fractions to the DIL in combination with androgen deprivation therapy. Genitourinary (GU) and rectal toxicity, International Prostate Symptom Score (IPSS) and IPSS quality of life (IPSS-QOL) score were collected.

Results: Forty-five patients with a median follow-up of 20 months were analyzed. The cumulative incidence of acute grade ≥ 2 GU and rectal toxicity was 33.1% and 9.5%, respectively. Regarding late toxicity, the cumulative incidence of grade ≥ 2 GU and rectal toxicity was 12.6% and 2.8%, respectively. During treatment, the mean increase of IPSS was +7.4 ± 4.2 and the mean increase of IPSS-QOL was +1.7 ± 1.3. However, both IPSS and IPSS-QOL scores returned to their baseline levels by 3-months post-treatment. No significant correlation between baseline characteristics and grade ≥ 2 GU or rectal toxicity was found.

Conclusion: Focal SIB to the DIL of ≥ 90 Gy EQD2 in unfavorable intermediate to high-risk prostate cancer patients resulted in tolerable toxicity profiles. The mean IPSS and IPSS-QOL scores both worsened during treatment; however, both scores returned to baseline level by 3 months after treatment.

Key words: feasibility; safety; volumetric modulated arc therapy; simultaneous integrated boost; dominant intraprostatic lesion; prostate cancer

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Introduction

Although radiotherapy is considered the standard of care for localized prostate cancer treatment, there is still a significant rate of local relapse which were 9.8% and 14.6% for intermediate and high risk, respectively [1]. The location of recurrence is predominantly at the same site as the dominant baseline tumor [2, 3]. Chopra, et al. [4] reviewed patient databases to identify predictive factors for

local recurrence after external beam radiation therapy (EBRT), and their results showed that 95% of patients recurred at the original site of dominant percentage core length (PCL). A study by Arrayeh, et al. [5] reported that up to 89% of recurrent tumors occurred at the same location as the dominant baseline tumors. Therefore, it was proposed that intensification of focal treatment to the dominant intraprostatic lesion (DIL) may enhance local tumor control [5].

To identify DILs, multiparametric magnetic resonance imaging (mpMRI) consisted of T2W and diffusion-weighted imaging (DWI) is generally used [6]. Several retrospective studies reported a favorable outcome of dose escalation to the DILs targeted by mpMRI [7, 8]. A meta-analysis [9] that included retrospective studies (most of which used a boost dose to the DIL of ≥ 90 Gy) reported a median disease-free survival (DFS) rate of 95%, and late grade ≥ 2 gastrointestinal (GI) and genitourinary (GU) toxicity of 3% and 12%, respectively. It was, therefore, concluded that ultra-high boost dose to the DIL [≥ 90 Gy equivalent dose in 2Gy fractions (EQD2)] is safe and effective. Safety analyses from several prospective studies [10–12] and a meta-analysis [13] showed acceptable toxicity rates. The FLAME randomized phase III trial [14] compared outcomes between EBRT with a dose to the entire prostate of 77 Gy in 35 fractions with an additional boost of 95 Gy to the DIL. Biochemical DFS was significantly higher in the focal boost arm compared to the standard arm. However, there was no significant difference in grade ≥ 2 late GU and GI toxicity. Although the result of dose escalation to the DIL appears to be safe with improved biochemical control, this technique is not recognized as or recommended to be the standard of care in the guidelines due to little strong evidence and lack of long-term outcomes. Accordingly, the aim of this study was to investigate the feasibility and safety of definite volumetric modulated arc therapy (VMAT) with simultaneous integrated boost (SIB) to the DIL in patients with unfavorable intermediate to high-risk prostate cancer.

Materials and methods

This study was conducted at the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University,

Bangkok, Thailand during December 2018 to April 2021. Patients who had biopsy-proven intermediate to high risk prostate cancer with pre-treatment mpMRI study were eligible for inclusion. Lesions defined as PI-RADS (Prostate Imaging-Reporting and Data System, version 2.0) 4 or 5 were classified as a DIL [15, 16]. The exclusion criteria were evidence of lymph node or distant metastasis, trans-urethral resection of the prostate (TURP), prostatectomy, prior pelvic irradiation, and secondary malignancy. This single-arm uncontrolled clinical trial evaluated GU and rectal toxicity outcomes of fractionated EBRT and SIB to the DIL with the dose of 87.75 Gy (2.25 Gy/F) or 70 Gy (3.5 Gy/F), and to the entire prostate gland of 78 Gy (2 Gy/F) or 60 Gy (3 Gy/F). The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 691/2018), and all enrolled patients gave written informed consent to participate.

Patients were implanted with three fiducial markers at least 2 weeks prior to computed tomography (CT) simulation. CT simulation was performed using 1 mm slice thickness, and the reconstructed CT images were adapted using iterative metallic artifact reduction (iMAR) software (Siemens Healthineers, Erlangen, Germany). MRI simulation consisted of T2W, DWI, and apparent diffusion coefficient (ADC) images. For patients having mpMRI prior to the date of simulation no more than 3 months, MRI simulation was optional. DILs were identified by a specialized diagnostic radiologist (WT) using mpMRI and/or MRI simulation images fusion with CT simulation by rigid registration. A planning target volume (PTV) margin of 5 mm was added around the prostate gland, seminal vesicles (SV), and DILs in all directions except posterior, which had 3 mm added. The dose prescription was 78 Gy (2 Gy/F) or 60 Gy (3 Gy/F) to the prostate gland with an additional boost up to 87.75 Gy (2.25 Gy/F) or 70 Gy (3.5 Gy/F) to DILs. The dose to the SVs depended on their risk of involvement. Without SV invasion, a dose of 60 Gy in 39 fractions or 50 Gy in 20 fractions was prescribed. If there was SV involvement (T3b), the prescribed dose was similar to that of the prostate gland for one or both sides depending on the extent of involvement. VMAT technique with SIB was planned with the dose constraints shown in Supplementary Table 1. Patients were treated during weekdays and daily position verification based on implanted fiducial mark-

Table 1. Patient baseline clinical characteristics

Patient characteristics	Number of patients (n = 45)
Initial PSA [ng/mL]	
< 10	12 (26.7%)
10–20	40%
> 20	15 (33.3%)
Gleason Score (grade group)	
3 + 3 (grade group1)	4 (8.9%)
3 + 4 (grade group2)	16 (35.6%)
4 + 3 (grade group3)	14 (31.1%)
4 + 4, 3 + 5, 5 + 3 (grade group4)	6 (13.3%)
4 + 5, 5 + 4, 5 + 5 (grade group5)	5 (11.1%)
Clinical T staging	
T2a	12 (26.7%)
T2b	1 (2.2%)
T2c	24 (53.3%)
T3a	2 (4.4%)
T3b	6 (13.3%)
NCCN risk group	
Unfavorable intermediate risk	3 (6.7%)
High risk	16 (35.5%)
Very high risk	26 (57.8%)
ADT	
Bilateral orchidectomy	2 (4.4%)
GnRH agonist/antagonist	43 (95.6%)
Baseline IPSS	
1–7 (mild)	27 (60%)
8–19 (moderate)	17 (37.8%)
20-35 (severe)	1 (2.2%)
Location of DIL	
Peripheral zone	37 (56.1%)
Transitional zone	19 (28.8%)
Central zone	10 (15.1%)
Number of DIL	
1	36 (80%)
2	7 (15.6%)
3	2 (4.4%)
DIL volume [mL]	
< 1	26 (57.8%)
1–2	9 (20%)
> 2	10 (22.2%)
PTV DIL volume [mL]	
< 10	31 (68.9%)
> 10	14 (31.1%)

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Patient characteristics	Number of patients (n = 45)
Prostate volume [mL]	
< 30	10 (22.2%)
30–60	27 (60%)
> 10	8 (17.8%)
PI-RADS	
PI-RADS 4	24 (53.3%)
PI-RADS 5	21 (46.7%)

PSA — prostate-specific antigen; NCCN — National Comprehensive Cancer Network; ADT — androgen deprivation therapy; IPSS — International Prostate Symptom Score; DIL — dominant intraprostatic lesion; PTV — planning target volume; PI-RADS — Prostate Imaging-Reporting and Data System

ers was performed using an in-room X-ray based monitoring system (ExacTrac®; BRAINLAB AG, Feldkirchen, Germany). The position verification protocol was daily ExacTrac® evaluation in every fraction and cone-beam CT (CBCT) scan during first 3 fractions, followed by 2 times per week for the first 2 weeks, and then weekly.

Patient were followed up weekly during treatment, then at one month, and every three months thereafter. Toxicity profiles were evaluated according to the Common Toxicity Criteria for Adverse Event (CTCAE) version 5.0 [17]. Severity of urinary symptoms and quality of life (QOL) were assessed according to the International Prostate Symptom Score (IPSS) system (Thai version) [18]. The primary endpoint in this study was GU and rectal toxicity, and the secondary endpoint was changes in IPSS and quality of life (IPSS-QOL) due to urinary symptom during and after treatment.

Sample size calculation and statistical analysis

Using a previously reported rate of late GU toxicity of 27% in the DIL boost arm [19] and an error in the event rate of 50%, a total sample size of 45 patients was calculated using nQuery Advisor software (Statistical Solutions, Cork, Ireland). STATA version 14.0 (StataCorp, College Station, TX, USA) was used for all other statistical analyses. The median follow-up time was measured from the end of radiotherapy to the time of analysis. Categorical variables were compared using chi-square test or Fisher's exact test, and those results are shown as number and percentage. Comparisons of continu-

ous data with normal distribution were made using Student's *t*-test, and using Mann-Whitney U test for non-normally distributed data. The results of those comparisons are shown as mean with standard deviation and median with interquartile range for normally and non-normally distributed continuous data, respectively. The cumulative incidence of toxicity was analyzed using Cox proportional hazards regression model. IPSS and IPSS-QOL scores were analyzed using descriptive analysis. A p-value less than 0.05 was considered statistically significant for all tests.

Results

A total 45 patients who completed radiation therapy in 39 fractions (32 patients) or 20 fractions (13 patients) with a median follow-up time of 20 months [interquartile range (IQR): 10–25] were included. Target and organs at risk (OAR) doses for each scheme are shown in Supplementary Tables 2 and 3. The median age of patients was 76 years (IQR: 71.5–80.5), and the median prostate-specific antigen (PSA) level was 12.3 ng/ml (IQR: 8.6–23.7). According to the National Comprehensive Cancer Network (NCCN) risk classification, most patients were in the high-risk group (32 patients, 71%). For Tumor–Node–Metastasis (TNM) staging, 19 patients (42.2%) were T2a–T2c, and 26 patients (57.8%) were T3a–T3b. All patients received androgen deprivation therapy (ADT) by GnRH agonists (95.6%) or bilateral orchidectomy (4.4%). For DIL characteristics, most of the patients (80%) had one lesion and the most common location was the peripheral zone which was 56.1%. The median DIL volume was 0.7 ml (IQR: 0.3–1.8), and the median prostate volume was 41.8 ml (IQR: 30.2–54.8). According to PI-RADS classification, DILs were defined as PI-RADS 4 and PI-RADS 5 in 24 patients (53.3%) and 21 patients (46.7%), respectively. Baseline patient clinical characteristics are shown in Table 1.

Acute GU toxicity mainly manifested as urinary urgency, urinary frequency, nocturia, and dysuria. No patients developed gross hematuria. Most patients (32 patients, 71.1%) experienced grade 0 to 1 acute GU toxicity. There were 12 patients (26.7%) and one patient (2.2%) who developed grade 2 and grade 3 GU toxicity, respectively. The cumulative incidence of acute grade ≥ 2 GU toxicity was

33.1%. The actuarial rate of acute grade ≥2 GU toxicity was 28.1% and 30.7% in the conventional fractionation cohort and moderate hypofractionation cohort, respectively (p = 0.35). Late GU toxicity mainly manifested as urinary frequency and nocturia. There were 41 patients (91.1%) and 4 patients (8.9%) who developed grade 1 and 2 late GU toxicity — there was no grade 3 or higher. The cumulative incidence of late grade ≥ 2 GU toxicity was 12.6%.

Proctitis was the most common manifestation of acute rectal toxicity. One patient (2.2%) developed grade 3 acute rectal toxicity, and 3 patients (6.7%) developed grade 2 acute rectal toxicity. The cumulative incidence of acute grade ≥ 2 rectal toxicity was 9.5%. The actuarial rate of acute grade ≥ 2 rectal toxicity was non-significantly higher in the moderate hypofractionation cohort than in the conventional fractionation cohort which is (15.3% *vs.* 6.3%, respectively; p = 0.80). For late rectal toxicity, one patient (2.2%) had grade 2 rectal toxicity, and no patients had grade 3 or higher toxicity. The cumulative incidence of late grade ≥ 2 rectal toxicity was 2.8%. No baseline patient clinical characteristics were found to be correlated with acute or late grade ≥ 2 toxicity. Graphs showing the trends of grade ≥ 2 GU and rectal toxicity at each follow-up visit are shown in Figure 1AB.
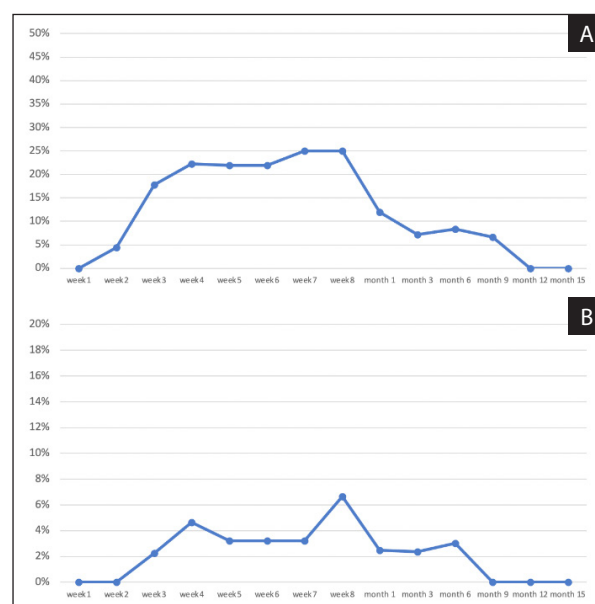

Figure 1. Percentage of patients having grade ≥ 2 genitourinary (**A**) and rectal (**B**) toxicity at each visit
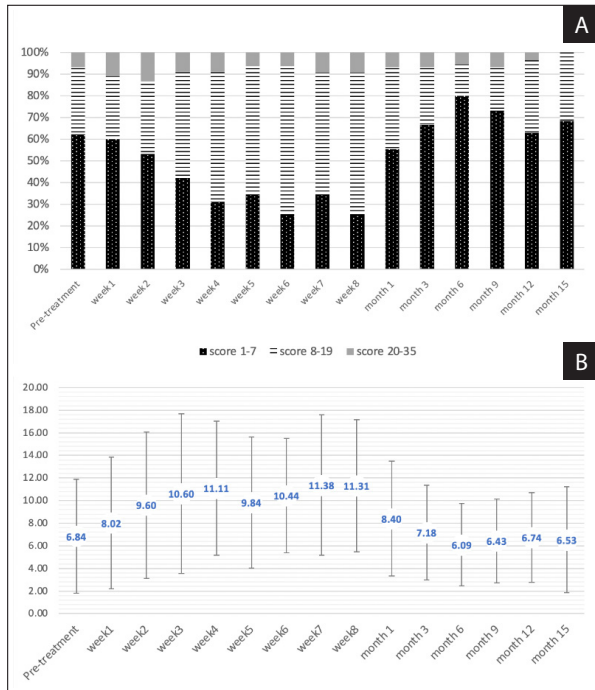
Figure 2. Percentage of patients stratified by severity scoring of International Prostate Symptom Score (IPSS) (mild 1–7, moderate 8–19, and severe 20–35) (**A**), and mean IPSS severity score at each visit (**B**)
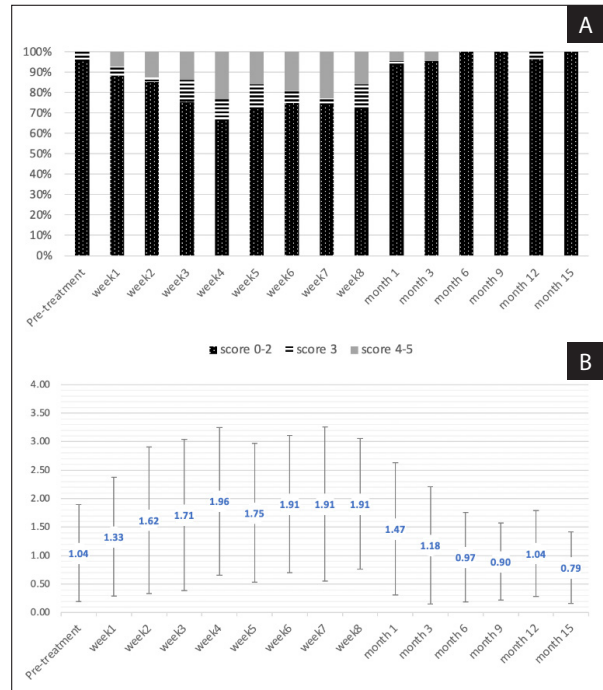

Figure 3. Percentage of patients stratified by satisfaction score of International Prostate Symptom Score (IPSS) quality of life (IPSS-QOL) (pleasant 0–2, uncertain 3, and unpleasant 4–5) (**A**), and mean IPSS-QOL satisfaction score at each visit (**B**)

The IPSS at baseline before treatment was mild, moderate, and severe in 27 of 45 patients (60%), 17 patients (37.8%), and 1 patient (2.2%), respectively. The IPSS stratified by severity at each follow-up visit is shown in Figure 2A. During treatment, the scores gradually increased overtime, as shown in Figure 2B. The mean change in IPSS during treatment were +7.4 ± 4.2 points; however, at 3 months after treatment, the IPSS returned to its baseline level (Figure 2B). The mean IPSS at baseline was 6.8 ± 5.0, and the mean IPSS at 3 months was 7.2 ± 4.2 (p = 0.44).

Regarding overall IPSS-QOL scoring, all 45 patients reported a score that fell within the pleasant range. However, during treatment, 7 patients (15.5%) rated the score in the uncertain range (score 3), and 16 patients (35.5%) rated the score in the unpleasant range (score 4 to 5). IPSS-QOL stratified by level of satisfaction at each follow-up visit is shown in Figure 3A. The IPSS-QOL score increased during treatment by a mean change of +1.7 ± 1.3 points. The mean IPSS-QOL score at each follow-up visit is shown in Figure 3B. The mean IPSS-QOL score at baseline was 1.0±0.9 points, and the mean IPSS-QOL score at 3 months was 1.2 ± 1.0 points (p = 0.82).

Discussion

This study, to the best of our knowledge, is the first study to investigate the feasibility of definite VMAT with SIB to the DIL of ≥ 90 Gy EQD2 in patients with unfavorable intermediate to high-risk prostate cancer. Our results showed acceptable levels of toxicity rates and QOL.

The rationale behind the dose fractionation evaluated in this study was derived from a meta-analysis [9] that suggested a boost dose to the DIL of ≥ 90 Gy EQD2. The results in that study showed an impressive biochemical outcome and acceptable rates of GI and GU toxicity. Moreover, the boost dose to the DIL in a randomized phase III study (the FLAME trial [14]) was 95 Gy, which is equivalent to 107 Gy EQD2 ($\alpha/\beta = 3$), and the outcome demonstrated a significant improvement in biochemical DFS. At the beginning of the present study, the dose fractionation was 78 Gy (2 Gy/F) with a DIL boost of 87.75 Gy (2.25 Gy/F) which is equivalent to a dose of 92 Gy EQD2 ($\alpha/\beta = 3$); however, the protocol was amended to a dose of 60 Gy (3 Gy/F) to the prostate, and 70 Gy (3.5 Gy/F) to the

Table 2. Radiation dosing and toxicity outcomes compared among the present study and previous studies that supplemented external beam radiation therapy (EBRT) with simultaneous integrated boost (SIB) to the dominant intraprostatic lesion (DIL)

	Fonteyne et al (2008) [10]	Schild et al (2014) [7]	Ippolito et al (2015) [12]	FLAME trial (2020) [14]	Present study
Prostate dose (boost dose)	78 Gy (81–82 Gy)	75.6–77.4 Gy (83 Gy)	72 Gy (80 Gy)	77 Gy (95 Gy)	78 Gy/60 Gy (87.75 Gy/70 Gy)
No. patients	230	78	40	571	45
Median F/U	9 months	36 months	19 months	72 months	20 months
Acute GU toxicity	Grade 2 = 41% Grade 3 = 7% No grade 4	Grade 2 = 53% No grade 3–4	Grade 2 = 30% Grade 3 = 2.5% No grade 4	≥ grade 2 = 42.3%* (Report in 2007) [23]	Grade 2 = 26.7% Grade 3 = 2.2% No grade 4
Acute GI toxicity	Grade 2 = 11% No grade 3–4	Grade 2 = 19% No grade 3–4	Grade 2 = 15% Grade 3 = 5% No grade 4	≥ grade 2 = 14.8%* (Report in 2007) [23]	Grade 2 = 6.7% Grade 3 = 2.2% No grade 4
Late GU toxicity	N/A	Grade 2 = 26% Grade 3 = 3% No grade 4	Grade 2 = 5% Grade 3 = N/A Grade 4 = 2.5%	≥ grade 2 = 28%	Grade 2 = 8.9% No grade 3–4
Late GI toxicity	N/A	Grade 2 = 4% Grade 3 = 0% No grade 4	Grade 2 = 2.5% Grade 3 = 2.5% No grade 4	≥ grade 2 = 13%	Grade 2 = 2.2% No grade 3–4

GU — genitourinary; GI — gastrointestinal

DIL which is equivalent to 91 Gy EQD2 ($\alpha/\beta = 3$). The reason for the aforementioned change was to adopt hypofractionation into clinical practice at our center.

For DIL characteristics in this study, DILs were mostly located at the peripheral zone, and the mean DIL volume was 1.8 mL or 3.7% of prostate volume, which is slightly lower than the DIL volume reported in a meta-analysis [9] that reported a median DIL volume of 2.4 mL or 7% of prostate volume. The median number of DILs was one lesion, which is comparable to other studies in DIL identification [20, 21]. PTV of DIL was added with 5–10 mm margin in most trials, but in this study, we used 5 mm in all directions, except 3 mm for the posterior margin. A smaller margin was applied due to ability to identify intrafraction motion by ExacTrac®. If snap verification showed movement beyond 3 mm tolerance, the treatment was stopped and repositioning was performed.

The toxicity profiles were shown to have acceptable rates in this study. GU toxicity was comparable to the outcome from FLAME trial [14] (12.6% and 12%). However, late rectal toxicity in our study was lower (2.8% *vs.* 13%). One possible explanation is that the median follow-up time in this study was shorter. Comparing toxicity to other phase II studies [7, 10, 12] (Tab. 2), the acute and late GU and rectal toxicity reported in this study were slightly lower. The use of daily ExacTrac® and a smaller PTV margin could have resulted in a lower rate of toxicity compared with other studies.

We had one patient who developed grade 3 rectal toxicity, which was hematochezia, at week 8 of treatment. Dose volume histogram (DVH) of rectum was V65 of 11.9%, and V40 of 34.78%, which passed the protocol. However, Dmax of rectum in this patient was 87.8 Gy, which was the highest dose among 45 patients. Fonteyne, et al. [10] used rectal Dmax < 76 Gy as the dose constraint. Since rectal Dmax was not a dose constraint in our study, rigorous consideration of rectal Dmax was of less concerned. Moreover, the DIL in this case involved peripheral zone located anterior to the rectum, which could result in higher risk of the rectum to be in a very high dose region. Confirmed by CBCT, as shown in Figure 4, two CBCT images taken in two separate weeks showed an enlarged rectum, which caused by increased amount of feces. Therefore, there was a higher probability for this patient to develop grade 3 rectal toxicity.

For IPSS and IPSS-QOL, the questionnaires used in this study was a Thai language version that was translated from the original version, and it
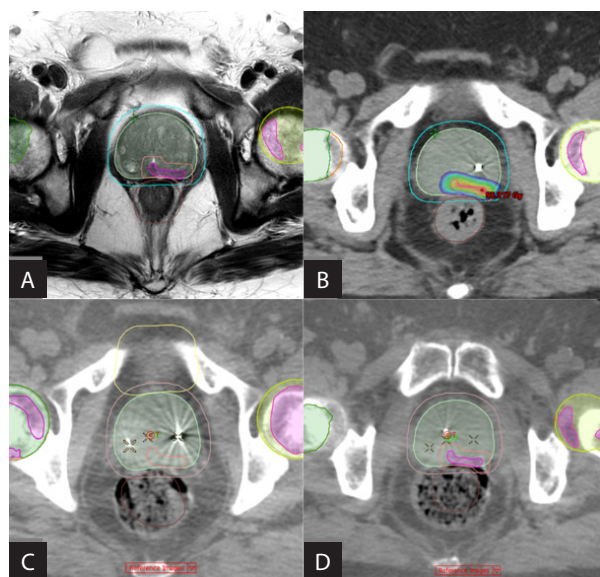
Figure 4. Target delineation of the dominant intraprostatic lesion (DIL) (**A**). Radiation dose of 87.75 Gy (**B**) and cone-beam computed tomography (CBCT) images (**CD**) from patient number 8

was validated for reliability [18]. In this study, the majority of patients had mild to moderate severity of IPSS. Although the IPSS significantly increased during treatment, after 3 months, the median IPSS decreased back to the baseline level. The same trend in IPSS was also observed in another study [22], and it is considered a good subjective outcome that can be used to monitor urinary symptoms in prostate cancer patients. Malik, et al. [22] found a high IPSS (score ≥ 15) to be significantly associated with a higher incidence of grade ≥ 2 GU toxicity. However, in this study, IPSS at baseline was lower, and no significant correlation was found between severity of IPSS and GU toxicity. For IPSS-QOL, the trend of changes in the score was similar to that of IPSS which also demonstrated in the study from Aghdam N et al. The trend of QOL was worse during radiotherapy but regained to baseline at 3 months thereafter [23].

A strength of this study is that we used self-reported outcomes (IPSS and IPSS-QOL score) that accurately reflect the severity of patient symptoms. Another strength was the homogeneity of treatment. There was a defined protocol for CT simulation, target delineation, treatment delivery, image-guided radiation therapy (IGRT), and follow-up scheme. For target delineation, DILs were contoured by a radiologist who specializes in pros-

tate imaging, which would be expected to result in high reproducibility. The main limitation of this study is the small number of patients and the short follow-up time. Since there was evidence from the FLAME trial [14] of improved biochemical control and this dose prescription appears to be safe and feasible, further research on DIL boost will be conducted.

Conclusion

Focal SIB to the DIL of ≥ 90 Gy EQD2 in unfavorable intermediate to high-risk prostate cancer patients resulted in tolerable toxicity profiles. Although, IPSS and IPSS-QOL scores were worsening during treatment, at 3 months after treatment, the scores declined to be equivalent to the baseline values.

Patient consent statement
Authors confirm that the protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 691/2018), and all enrolled patients gave written informed consent to participate.

References

1. Zumsteg ZS, Spratt DE, Romesser PB, et al. Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose Escalation Era of External Beam Radiotherapy for Prostate Cancer. J Urol. 2015; 194(6): 1624–1630, doi: 10.1016/j.juro.2015.06.100, indexed in Pubmed: 26165583.

2. Pucar D, Hricak H, Shukla-Dave A, et al. Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence. Int

J Radiat Oncol Biol Phys. 2007; 69(1): 62–69, doi: 10.1016/j.ijrobp.2007.03.065, indexed in Pubmed: 17707266.

3. Mendez LC, Ravi A, Chung H, et al. Pattern of relapse and dose received by the recurrent intraprostatic nodule in low- to intermediate-risk prostate cancer treated with single fraction 19 Gy high-dose-rate brachytherapy. Brachytherapy. 2018; 17(2): 291–297, doi: 10.1016/j.brachy.2017.10.001, indexed in Pubmed: 29137956.

4. Chopra S, Toi A, Taback N, et al. Pathological predictors for site of local recurrence after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2012; 82(3): e441–e448, doi: 10.1016/j.ijrobp.2011.05.035, indexed in Pubmed: 22284038.

5. Arrayeh E, Westphalen AC, Kurhanewicz J, et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal MRI and MRSI study. Int J Radiat Oncol Biol Phys. 2012; 82(5): e787–e793, doi: 10.1016/j.ijrobp.2011.11.030, indexed in Pubmed: 22331003.

6. Tan CH, Hobbs BP, Wei W, et al. Diffusion-weighted MRI in the detection of prostate cancer: meta-analysis. AJR Am J Roentgenol. 2012; 199(4): 822–829, doi: 10.2214/AJR.11.7805, indexed in Pubmed: 22997374.

7. Schild MH, Schild SE, Wong WW, et al. Early Outcome of Prostate Intensity Modulated Radiation Therapy (IMRT) Incorporating a Simultaneous Intra-Prostatic MRI Directed Boost. OMICS J Radiol. 2014; 3(4), doi: 10.4172/2167-7964.1000170, indexed in Pubmed: 25717423.

8. Miralbell R, Mollà M, Rouzaud M, et al. Hypofractionated boost to the dominant tumor region with intensity modulated stereotactic radiotherapy for prostate cancer: a sequential dose escalation pilot study. Int J Radiat Oncol Biol Phys. 2010; 78(1): 50–57, doi: 10.1016/j.ijrobp.2009.07.1689, indexed in Pubmed: 19910135.

9. von Eyben FE, Kiljunen T, Kangasmaki A, et al. Radiotherapy Boost for the Dominant Intraprostatic Cancer Lesion-A Systematic Review and Meta-Analysis. Clin Genitourin Cancer. 2016; 14(3): 189–197, doi: 10.1016/j.clgc.2015.12.005, indexed in Pubmed: 26768965.

10. Fonteyne V, Villeirs G, Speleers B, et al. Intensity-modulated radiotherapy as primary therapy for prostate cancer: report on acute toxicity after dose escalation with simultaneous integrated boost to intraprostatic lesion. Int J Radiat Oncol Biol Phys. 2008; 72(3): 799–807, doi: 10.1016/j.ijrobp.2008.01.040, indexed in Pubmed: 18407430.

11. Sundahl N, De Meerleer G, Villeirs G, et al. Combining high dose external beam radiotherapy with a simultaneous integrated boost to the dominant intraprostatic lesion: Analysis of genito-urinary and rectal toxicity. Radiother Oncol. 2016; 119(3): 398–404, doi: 10.1016/j.radonc.2016.04.031, indexed in Pubmed: 27162160.

12. Ippolito E, Mantini G, Morganti AG, et al. Intensity-modulated radiotherapy with simultaneous integrated boost to dominant intraprostatic lesion: preliminary report on toxicity. Am J Clin Oncol. 2012; 35(2): 158–162, doi: 10.1097/COC.0b013e318209cd8f, indexed in Pubmed: 21336090.

13. Bauman G, Haider M, Van der Heide UA, et al. Boosting imaging defined dominant prostatic tumors: a systematic review. Radiother Oncol. 2013; 107(3): 274–281, doi: 10.1016/j.radonc.2013.04.027, indexed in Pubmed: 23791306.

14. Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. J Clin Oncol. 2021; 39(7): 787–796, doi: 10.1200/JCO.20.02873, indexed in Pubmed: 33471548.

15. Purysko AS, Rosenkrantz AB, Turkbey IB, et al. PI-RADS Version 2: A Pictorial Update. Radiographics. 2016; 36(5): 1354–1372, doi: 10.1148/rg.2016150234, indexed in Pubmed: 27471952.

16. Bastian-Jordan M. Magnetic resonance imaging of the prostate and targeted biopsy, Comparison of PIRADS and Gleason grading. J Med Imaging Radiat Oncol. 2018; 62(2): 183–187, doi: 10.1111/1754-9485.12678, indexed in Pubmed: 28990727.

17. Common Terminology Criteria for Adverse Events (CTCAE) [Internet]. Cancer Therapy Evaluation Program (CTEP). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (2020 Feb 10).

18. Nontakaew K, Kochakarn W, Kijvika K, et al. Reliability of a Thai version of the International Prostate Symptom Score (IPSS) for the Thai population. J Med Assoc Thai. 2014; 97(6): 615–620, indexed in Pubmed: 25137878.

19. Monninkhof EM, van Loon JWL, van Vulpen M, et al. Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial. Radiother Oncol. 2018; 127(1): 74–80, doi: 10.1016/j.radonc.2017.12.022, indexed in Pubmed: 29336835.

20. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol. 2011; 59(4): 477–494, doi: 10.1016/j.eururo.2010.12.009, indexed in Pubmed: 21195536.

21. Crook J, Ots A, Gaztañaga M, et al. Ultrasound-planned high-dose-rate prostate brachytherapy: dose painting to the dominant intraprostatic lesion. Brachytherapy. 2014; 13(5): 433–441, doi: 10.1016/j.brachy.2014.05.006, indexed in Pubmed: 24958556.

22. Malik R, Jani AB, Liauw SL. External beam radiotherapy for prostate cancer: urinary outcomes for men with high International Prostate Symptom Scores (IPSS). Int J Radiat Oncol Biol Phys. 2011; 80(4): 1080–1086, doi: 10.1016/j.ijrobp.2010.03.040, indexed in Pubmed: 20643513.

23. Aghdam N, Pepin A, Buchberger D, et al. Stereotactic Body Radiation Therapy (SBRT) for Prostate Cancer in Men With a High Baseline International Prostate Symptom Score (IPSS ≥ 15). Front Oncol. 2020; 10: 1060, doi: 10.3389/fonc.2020.01060, indexed in Pubmed: 32719744.