Dosimetric Differences between Scheduled and Adapted Plans Generated from Ethos Adaptive Radiotherapy for Patients with Prostate Cancer

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การเปรียบเทียบปริมาณรังสีระหว่างแผนการรักษา 2 แบบที่ใช้ในการรักษาผู้ป่วยมะเร็งต่อมลูกหมากด้วยเครื่องอีธอส

น.ส.สริตา สุวีระ

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ในทางรังสีรักษาและมะเร็งวิทยา ต่อมลูกหมากเป็นหนึ่งในอวัยวะที่อาจมีการเคลื่อนที่ได้ในระหว่างแต่ละครั้งของการรักษา เนื่องจากตำแหน่งของอวัยวะอยู่ใกล้กับกระเพาะปัสสาวะและทวารหนักที่มีการเปลี่ยนแปลงได้ง่าย การฉายรังสีที่มีระบบปรับแต่งแก้ไขแผนการรักษา หรือ adaptive radiotherapy จึงมีส่วนช่วยสำคัญในการลดความไม่แน่นอนของการเปลี่ยนแปลงดังกล่าวและสามารถช่วยลดผลข้างเคียงจากรังสีกับผู้ป่วยได้ จุดประสงค์ของงานวิจัยครั้งนี้คือเพื่อตรวจสอบประสิทธิภาพของการรักษาผู้ป่วยมะเร็งต่อมลูกหมากด้วยวิธี adaptive radiotherapy โดยเปรียบเทียบความแตกต่างของแผนการรักษาสองแบบได้แก่ scheduled plan และ adapted plan ที่ถูกสร้างและคำนวณจากเครื่อง Ethos จึงได้ทำการเก็บข้อมูลของการรักษาทั้งหมดจำนวน 100 ครั้งจากผู้ป่วยมะเร็งต่อมลูกหมากที่เคยได้รับการรักษาด้วยเครื่องฉายรังสี Ethos โดยข้อมูลประกอบด้วย PTVs D95%, PTV D_{min}, PTV D_{max}, ปริมาณรังสีที่อวัยวะใกล้เคียง OAR doses of bladder and rectum, ค่าดัชนีความสม่ำเสมอของการกระจายรังสี หรือ homogeneity index (HI) และความถี่ของการเลือกแผนการรักษาแต่ละแบบ สำหรับ PTV1, PTV2 และ PTV3 นั้นมีปริมาณรังสีกำหนดอยู่ที่ 48 Gy, 57.6 Gy, และ 60 Gy ตามลำดับ ในการเปรียบเทียบพบว่า 77% ของจำนวนครั้งของการรักษาทั้งหมด adapted plan มีค่า PTV3 D95% ใกล้เคียง reference plan มากกว่า scheduled plan โดยมี 79% ของจำนวนครั้งที่ adapted plan มีค่า PTV3 D95% มากกว่า scheduled plan เฉลี่ยอยู่ที่ 0.2% ± 1.2% นอกจากนี้ยังพบว่า D_{min} จาก adapted plan มีค่าเฉลี่ยมากกว่า scheduled plan ในขณะที่มีค่าเฉลี่ยของ D_{max} และ HI จาก adapted plan น้อยกว่า scheduled plan ในผู้ป่วยทุกราย ยกเว้นผู้ป่วยหนึ่งรายที่ค่าเฉลี่ยของ D_{max} และ HI มากกว่าใน scheduled plan และสำหรับปริมาณรังสีที่กระเพาะปัสสาวะ จาก 100 ครั้งของการรักษา พบว่ามี 23 ครั้งที่มีค่า V60Gy เกินกว่าเกณฑ์แต่ adapted plan สามารถลดปริมาณรังสีเฉลี่ยถึง 0.71% ± 0.57% (*p*-value <0.001) สำหรับ V40.8Gy และ V48.6 Gy adapted plan สามารถลดปริมาณรังสีเฉลี่ยอยู่ที่ 0.08% ± 0.17% และ 0.11% ± 0.20% ตามลำดับ (*p*-value <0.001) ส่วนปริมาณรังสีที่ทวารหนักได้รับนั้น adapted plan สามารถลดปริมาณรังสี V20, V30, V40, V50 และ V60 Gy ลงเฉลี่ยถึง 1.47%, 4.83%, 5.70%, 12.09% และ12.52% ตามลำดับ โดยเฉพาะ V50 Gy ที่มีปริมาณรังสีเกินกว่าเกณฑ์ใน scheduled plan แต่ adapted plan สามารถลดปริมาณรังสีลงให้ต่ำกว่าเกณฑ์ได้ โดยสรุปแล้วพบว่า adapted plan ให้ผลของปริมาณรังสีสำหรับแผนการรักษาที่ดีกว่าและมีความแปรปรวนที่น้อยกว่าทั้งในส่วนของปริมาณรังสีที่ PTV, HI และ OAR โดยให้ค่าปริมาณรังสีที่สูงขึ้นใน D_{min} และลดลงที่ D_{max}, HI และ OAR ในขณะที่ adpated plan ให้ปริมาณรังสีใน PTVs D95% ใกล้เคียง reference plan มากกว่า scheduled plan ถึง 66% ของจำนวนครั้งในการรักษาทั้งหมด จึงทำให้เห็นว่า adapted plan สามารถพัฒนาแผนการรักษาได้อย่างมีนัยสำคัญ อย่างไรก็ตามแนวโน้มของการให้ปริมาณรังสีที่สูงของ adapted plan อาจจะทำให้มี hot area เกิดขึ้นในผู้ป่วยบางราย ดังนั้นการให้รังสีแพทย์ตรวจสอบแผนการรักษาทุกครั้งก่อนทำการฉายรังสีจึงยังมีความสำคัญและจำเป็น

สาขาวิชา	ฟิสิกส์การแพทย์	ลายมือชื่อนิสิต .....
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Prostate is one of the organs that can easily move or change during the treatment fractions. Adaptive radiotherapy can help to reduce the uncertainty of interfraction and decrease the side effects produced from the radiation given to the patients. The objective of this study was to provide evidence of the efficiency of adaptive radiotherapy for prostate cancer patients by investigating the dosimetric differences between the scheduled and adapted plans generated from Ethos. The treatment data of 100 fractions of prostate cancer patients who had previously been treated on Ethos daily adaptive radiotherapy were collected. The treatment data in each fraction of both scheduled and adapted plans include PTVs D95%, PTV D_{min}, PTV D_{max}, OAR doses of bladder and rectum, homogeneity index (HI) and frequency of plan selection were compared. The PTVs consist of PTV1, PTV2, and PTV3 which have dose prescription at 48 Gy, 57.6 Gy, and 60 Gy, respectively. PTV doses were compared in each fraction between scheduled and adapted plans. The adapted plan with 77% of all the fractions has the value of PTV3 D95% closer to the reference plan than the scheduled plan. There were 79% of fractions that the adapted plan had higher PTV3 D95% for 0.2% ± 1.2% on average than the scheduled plan in our study. The adaptation significantly pushed the average of D_{min} higher, lower the average of D_{max} and HI in every patient. Except for one patient that the average of D_{max} and HI index were higher than the scheduled plan. For bladder dose, there were 23 fractions that had values of V60Gy exceed the threshold, adaptation could lower the values for 0.71% ± 0.57% on average (*p*-value <0.001). For V40.8 Gy and V48.6 Gy, the adapted plan lowered the values for 0.08% ± 0.17% and 0.11% ± 0.20%, respectively (*p*-value <0.001). Overall, the adapted plan had the values less than the scheduled plan and both plans produced values below bladder constraints. Adaptation could reduce rectal dose of V20, V30, V40, V50, and V60 Gy for 1.47%, 4.83%, 5.70%, 12.09%, and 12.52%, respectively. Especially for V50 Gy that the value was higher than the rectal constraint in the scheduled plan but the adapted plan could lower it to within tolerance. In conclusion, the adapted plan produced better results and less variation in PTV doses, HI, and OAR doses, where it pushed the average of D_{min} higher and lower the average of D_{max}, HI, and OAR doses. In comparison with the scheduled plan, the adapted plan produced PTVs D95% closer to the reference plan for 66% of fractions. This showed significant improvements by the adaptation from Ethos. However, the higher dose of adapted plan over the reference plan might lead to creating some hot areas in target volume. Thus, a careful review by oncologists is required prior to dose delivery.

Field of Study:	Medical Physics	Student's Signature .....
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CHAPTER I

INTRODUCTION

1.1 **Background and rationale**

Adaptive radiotherapy has been widely performed in various hospitals nowadays, especially for treating patients with prostate cancer. It is efficient to adjust the treatment plan to the specific anatomy on each treatment day with the goal of improving the dose distribution to the target and sparing normal tissue. Prostate is one of the organs that can easily move or change during the treatment fractions because it is surrounded with bladder and rectum which contain unstable volume.[1] Adaptive radiotherapy can help to reduce the uncertainty of interfraction and decrease the side effects produced from the radiation given to the patients.

The workflow of adaptive radiotherapy on Ethos has more steps and is likely to spend more time during each fraction than a conventional treatment. It starts with CBCT image acquisition, followed by the CBCT images and CT simulation image matching, auto-segmentation, contour evaluation, plan generation, plan selection, QA calculation, and treatment delivery. In the step of plan generation, Ethos generates two different treatment plans which are scheduled and adapted plans. Only one of the plans that meet more clinical goals will be selected to perform the treatment on each day.

At King Chulalongkorn Memorial Hospital, adaptive radiotherapy performed on Varian's Ethos™ has recently been introduced and is available for clinical treatment in less than a year. So, this study aims to provide evidence of the efficiency of adaptive radiotherapy for prostate cancer patients by investigating the dosimetric differences between the scheduled and adapted plans generated from Ethos.

1.2 **Research question**

What are the dosimetric differences between scheduled and adapted plans generated from Ethos for patients with prostate cancer?

1.3 **Research objective**

To compare the dosimetric differences between scheduled and adapted plans generated from Ethos for patients with prostate cancer.

CHAPTER II

REVIEWED OF RELATED LITERATURES

2.1 **Theory**

2.1.1 Ethos™ adaptive radiotherapy

Ethos™ (Varian Medical System, Palo Alto, CA) adaptive radiotherapy is a treatment process that allows for the modification of a treatment plan based on the anatomy of the patient each day. It uses an artificial intelligence algorithm based on a convolutional neural network to do the auto-segmentation for the target organ and organ at risk structures.

After the auto contour has been reviewed by a radiologist, Ethos generates the scheduled and adapted plans. For the scheduled plan, the treatment plan is recalculated by rigidly registering the planning CT to the cone beam CT. There are three degrees of freedom for the couch movement including vertical, longitudinal, and lateral translation. It can not be adjusted manually after registration. The adapted plan is generated via Intelligent Optimized Engine™ (IOE). It reoptimizes the plan based on the new contour created by the auto segmentation. After the reoptimization for the adapted plan, the couch is unable to be moved or adjusted.

2.1.2 Rigid and deformable registration

The process of transformation occurs within a three-dimensional (3D) environment, where images are compared based on pixel or voxel properties, or by aligning the outlines of specific anatomical structures depicted in the images. Rigid registration, which is a global procedure, ensures that specific regions of the input image cannot be deformed independently from one another. As a result, the fusion achieved is a combination of the input and reference images, overlapping with each other.

Deformable registration is a computational technique that involves defining a function to measure the similarity between images and establishing a transformation model for the images under analysis. An optimization algorithm is applied to refine the

transformation model, aiming to maximize the similarity function. Several transformation models can be utilized in this process, including spline and demons, elastic, fluid, finite element model, and free form deformations.[2]

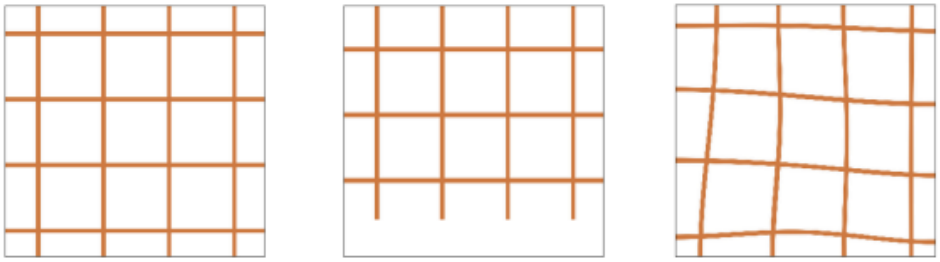


Figure 2.1 Examples of rigid and deformable transformations.

2.1.3 Treatment technique for prostate cancer radiotherapy

Radiotherapy has been a significant factor in the treatment of prostate cancer, providing an effective means to eliminate cancerous cells in the prostate. This treatment method utilizes powerful energy rays or particles to target and destroy the cancer cells. There are two primary techniques employed in radiotherapy for prostate cancer: brachytherapy and external beam radiotherapy. Brachytherapy involves the placement of small radioactive seeds within the patient's body and is commonly utilized for individuals with low to intermediate risk. On the other hand, external beam radiotherapy administers radiation from outside the body, projecting a beam directly onto the affected area. This technique is employed for patients across a range of risk levels, from low to very high.

In external beam radiotherapy, the advanced technique is essential for treating prostate cancer because the prostate can be very resistant to radiation while surrounded by the organs that are very sensitive to radiation like bladder and rectum. So, the common treatment techniques used for prostate cancer are intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc

therapy (VMAT). There are several studies that compare these two techniques in terms of target volume coverage, OAR sparing, and treatment time. A study conducted by Cem Onal et al.[3] compared the treatment outcomes of single-arc VMAT and 7-field IMRT techniques for prostate cancer patients. The findings of the study indicated that VMAT plans demonstrated comparable dosimetry to IMRT plans, with improved sparing of the rectum and bladder and a reduced requirement for monitor units (MUs). This is consistent with the results observed in the study by Penelope Knapp et al.[4], where VMAT was found to be superior in sparing OARs compared to 8-field IMRT. Furthermore, VMAT exhibited equivalent or superior target volume coverage compared to IMRT, as reported in studies.[5, 6] The positive outcomes observed, along with the verified reduction in treatment delivery time linked to VMAT, have led to the formulation and adoption of a clinical protocol.

2.1.4 Plan evaluation

Once the treatment planning phase is complete, each plan is subjected to an evaluation process. During this evaluation, specific criteria are established, taking into account the doses and volumes exposed to radiation. Evaluation tools such as dose distribution and dose volume histogram (DVH) are employed for this purpose. Objective evaluation methods are commonly utilized because assessing the three-dimensional dose distribution poses challenges. However, gaining a comprehensive understanding of its spatial characteristics remains a complex task, and the ability to personalize outcome predictions based on individual patient characteristics is still limited. This highlights the significance of standardized and systematic collection of clinical data and treatment outcomes following radiotherapy.

Additionally, it is important to note that the calculated dose distribution may not precisely reflect the actual dose delivered to the patient due to uncertainties in both dose calculation and treatment delivery. The evaluation of the calculated dose distribution often relies on the dose volume histogram, which summarizes the three-

dimensional dose information into two-dimensional metrics (dose and volume). To assess the adequacy of target coverage, DVH metrics are typically compared, and the presence of hot and cold regions is examined in relation to predetermined goal values defined in protocols..[7]

A dose volume histogram (DVH) is a visual depiction of the relationship between radiation dose and a specific volume of tissue in treatment planning. It is commonly used to compare multiple treatment plans for a given patient, providing insights into the uniformity of dose distribution within the target volume and highlighting potential areas of excessive radiation (hot spots) in critical normal tissues. DVHs are also valuable in radiobiology evaluations as they can be utilized to estimate the probability of tumor control (TCP) and the likelihood of complications in normal tissues (NTCP) by serving as input data.

The evaluation of dose distribution typically involves several approaches. This includes examining isodose curves on individual CT or MR slices of the treatment plan, visualizing isodose surfaces (three-dimensional representations of the isodose information), and analyzing DVH to assess the dose received by specific organs. These methods collectively contribute to a comprehensive evaluation of the radiation dose distribution.[8]

In the book "Radiation Oncology Physics: A Handbook for Teachers and Students," two types of dose volume histograms (DVHs) are described: direct (or differential) DVHs and cumulative (or integral) DVHs. Nevertheless, cumulative DVHs are more frequently employed as they offer the essential information required to calculate the area under the curve for dose levels surpassing 95% of the prescribed dose. In cumulative DVHs, the computer calculates the volume of the target that receives at least a specific dose and represents this volume (or percentage volume) against the corresponding dose on the plot. All cumulative DVH plots start at 100% of the volume for a dose of 0 Gy since the entire volume receives at least no dose.

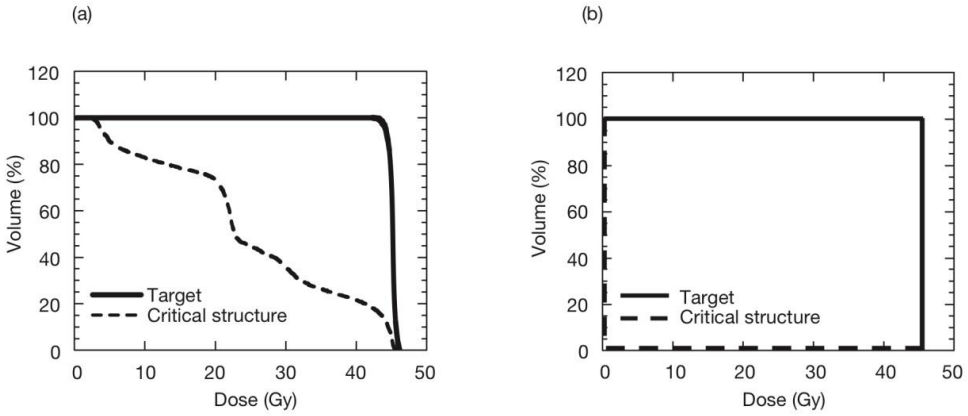


Figure 2.2 Example of cumulative DVHs displays are shown in (a) and the ideal cumulative DVHs is are shown in (b).

2.1.5 Gamma index

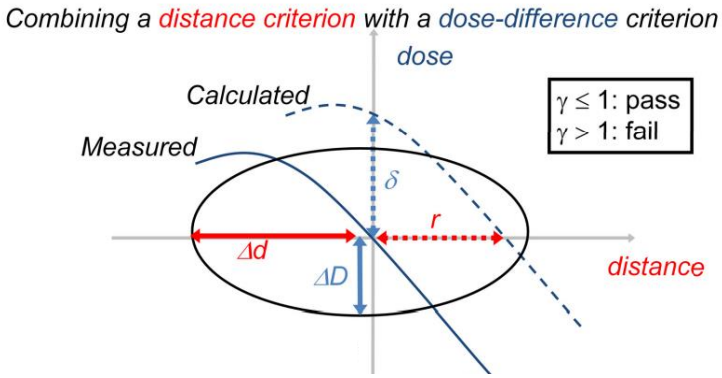


Figure 2.3 γ-evaluation comparing between calculation and measurement.

$$\gamma(\vec{r}_c, \vec{r}_m) = \sqrt{\frac{|\vec{r}_c, \vec{r}_m|^2}{DTA^2} + \frac{|D(\vec{r}_m) - D(\vec{r}_c)|^2}{\Delta D^2}} \qquad \begin{matrix} \gamma(r_m) \leqslant 1 & \text{Pass} \\ \gamma(r_m) > 1 & \text{Fail} \end{matrix}$$

The gamma index (γ) is a commonly used metric for verifying complex radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc radiotherapy (VMAT). It enables the comparison and evaluation of 2D dose distributions. The gamma index metric has received widespread recognition and is integrated into the majority of commercially available verification analysis software. It combines measurements of dose difference and distance-to-agreement, enabling efficient

analysis that proves particularly valuable in busy clinical environments. Patient-specific quality assurance through gamma analysis plays a crucial role in high-precision radiotherapy.[9] According to AAPM Task Group 218 recommendations, gamma passing rates should be equal to or greater than 95% for criteria involving a dose difference of 3%, a distance to agreement of 2 mm, and a threshold of 10%.

2.2 **Review of related literatures**

2.2.1 Varian ethos online adaptive radiotherapy for prostate cancer: Early results of contouring accuracy, treatment plan quality, and treatment time by Mikel Byrne et al.[10]

The objective of this study was to provide initial results regarding the precision of automated contouring, the quality of treatment plans, and the timing of treatment fractions in Ethos online adaptive radiotherapy for individuals diagnosed with prostate cancer. The research included a total of eighteen patients, encompassing both nonclinical and clinical groups. Regarding influencer contouring accuracy, it was found that no edits were necessary in 11% of all treatment fractions, while minor edits were required in 81% of fractions. In terms of target contouring accuracy, approximately 72% of clinical target volumes (CTVs) required no modifications, and 91% required either no changes or only minor adjustments.

For this research, intensity-modulated radiation therapy (IMRT) plans were created with 7, 9, or 12 fields for each case under investigation. The prescribed doses and limits for organs at risk were determined based on the eviQ guidelines, which served as clinical objectives for comparing the quality of treatment plans between scheduled and adaptive approaches. In the majority of treatment fractions (78%), the adaptive plan fulfilled a greater number of goals compared to the scheduled plan. For 15% of fractions, there was no difference in the number of goals achieved by the adaptive and scheduled plans. Interestingly, in 7% of fractions, the scheduled plan

outperformed the adaptive plan in terms of meeting more goals, as illustrated in Figure 2.4.

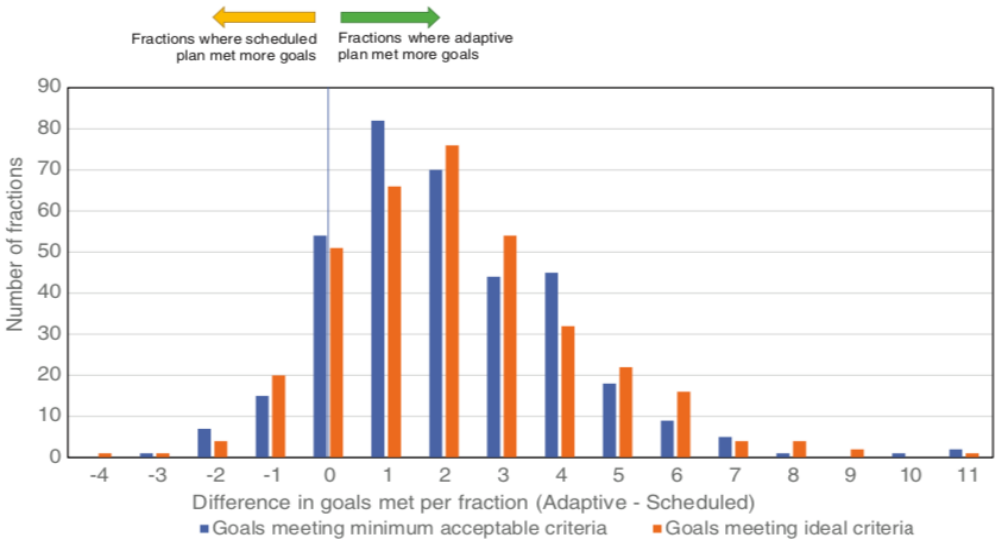


Figure 2.4 Histogram of differences in the number of planning clinical goals met per fraction.

Regarding the frequency of plan selection, the adaptive plan was chosen in 95% of all treatment fractions. However, there was a lower frequency of selecting the adapted plan for treatments targeting the prostate bed and nodes. In terms of timing data, it was observed that sites with a greater number of structures and more frequent contour editing required more time. It is anticipated that as the staff members gain more experience with the system, the fraction time will decrease.

From this study, it was noted that the adaptive plan had more goals met and was selected more frequently than the scheduled plan. However, the dosimetric differences in terms of homogeneity index between the scheduled and adaptive plans had not yet been observed.

2.2.2 Prospects for daily online adaptive radiotherapy via ethos for prostate cancer patients without nodal involvement using unedited CBCT auto-segmentation by Mojtaba Moazzezi et al.[11]

The objective of this study was to assess whether there is a dosimetric advantage in prostate adaptive radiation therapy when the Ethos auto-segmentation results were accepted without any

modifications. They firstly selected 25 prostate cancer patients who previously had been daily performing iCBCT and treated on a Halcyon. Then, new plans with 12-field IMRT were created for 54 Gy in 2 Gy fractions by the Ethos emulator. Only the first 10 fractions of each patient were simulated in the adaptation process on the Ethos emulator. The structures that had been auto-segmented included influencer structures, targets, and non-influencer organ at risk structures. Both scheduled and adapted plans were generated.

The comparison between the auto-segmented clinical target volume (CTV) without any editing and the CTV that had been manually edited by a radiologist was conducted by assessing the percent difference in volume. Out of 250 treatment fractions, the results indicated that the auto-segmented CTV volume was larger than the manually edited CTV volume in 74% of cases. Specifically, the auto-segmented CTV of the seminal vesicles within the CTV required volume reduction, while the intact prostate was generally accurately auto-segmented. In 96% of the 250 fractions, some form of editing was needed for the auto-segmentation. However, these edits were considered minor as they affected less than 10% of the volume. On average, the volume difference for the CTVs was 4.5%, and the minor edits constituted less than 10% of the total CTV volumes. One patient stood out as an outlier with substantial volume changes ranging from -25% to -50% due to under-contouring in the auto-segmentation, particularly in each fraction, an error was observed in the superior section of the prostate gland, where it coincided with the bladder. This error was detectable in the pretreatment imaging. Comparing the dose volume histograms between the auto-segmented CTV and the manually edited CTV in the adapted plan, small changes were observed. The changes were within 0.7% ± 4.5% for CTV-D98%, 0.3% ± 0.8% for bladder V90%, and 0.3% ± 1.5% for rectum V90%.

For the results of the dose volume histogram comparing between scheduled and adapted plans, shown in figure 2.5, adaptation increased CTV-true D98% by 2.9% ± 5.3% on average

for 24 patients. For the outlier, adaptation decreased values for CTV-true D98%.

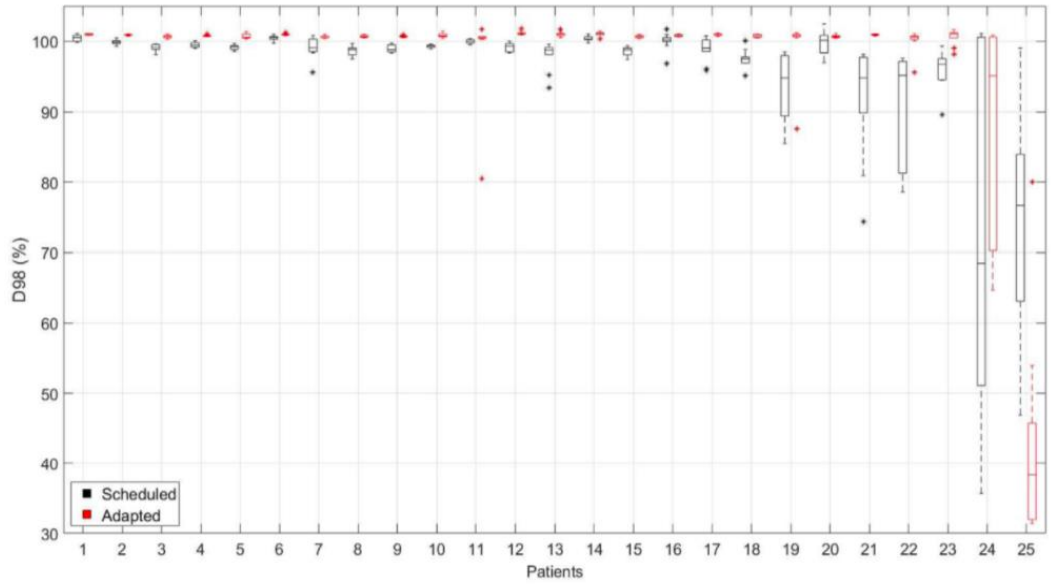


Figure 2.5 CTV-true D98% values for the 10 fractions per patient using the scheduled (black) versus adapted plans (red).

The comparison of bladder and rectum metrics at V50%, V75%, and V90% between the scheduled and adapted plans, it was shown a systematic decrease with adaptation for the bladder metrics. For bladder V75% and V90%, there were 2 fractions where the values were greater in the scheduled plan, but the adapted plan could lower it to within the threshold. For bladder V50%, there were 6 fractions where the adaptation pushed the values beyond the threshold. The metrics of rectum did not systematically improve with adaptation unless the values from the scheduled plan were greater than the threshold.

To summarize, the comparison between the scheduled and adapted plans revealed that the adapted plan, despite minor auto-segmentation errors, resulted in higher CTV doses in 92.5% of treatment fractions. Additionally, there was an improvement of 13.1% in bladder V90% (a measure of organ-at-risk sparing) and 6.5% in rectum V90%. Excluding the outlier case, the adapted CTV-

true D98% (a measure of dose coverage) averaged at 42.7% ± 14.8%.

2.2.3 Assessment of efficacy in automated plan generation for Varian Ethos intelligent optimization engine by Shyam Pokhare et al. [12]

The objective of this study was to evaluate the effectiveness of Varian Ethos IOE for automated planning and compare it with the Eclipse treatment planning system (TPS). A total of 36 retrospective cases involving the prostate and proximal seminal vesicles were chosen for analysis. The prescription dose for the proximal seminal vesicles was 50.4 Gy in 28 fractions, with a simultaneous integrated boost of 70 Gy for the prostate gland. Within the Ethos TPS, three treatment plans were automatically generated and then exported to the Eclipse TPS for comparison against a treatment plan based on radiotherapy intent. When normalizing the planning target volume (PTV) coverage, the Dmax% (maximum dose received) values were 108.8%, 108.1%, 108.4%, 109.6%, and 110.1% for the 2-full arc Eclipse plan, 9-field IMRT, 12-field IMRT, 2-full arc VMAT Ethos plans, and 2-full arc VMAT "Eclipse reoptimized" plans, respectively. Compared to the unnormalized plans, the average changes in Dmax% were 0.7%, 0.9%, -0.1%, and 0.01% for the 9-field IMRT, 12-field IMRT, 2-full arc VMAT Ethos plans, and 2-full arc VMAT "Eclipse reoptimized" plans, respectively.

The evaluation of organ-at-risk (OAR) indices was conducted for the Ethos plans, with reference to the Radiation Therapy Oncology Group report 0415 as a guideline. It was determined that the OAR indices were comparable among the Ethos plans as well as when compared to the Eclipse plans. Specifically, the Ethos 12-field IMRT plans demonstrated favorable adherence to most of the dosimetric objectives for treatment. For instance, the Bladder V64Gy values were 6.4%, 6.9%, 6.8%, 6.5%, and 6.5% for the 2-full arc Eclipse plan, 9-field IMRT, 12-field IMRT, 2-full arc VMAT Ethos plans, and 2-full arc VMAT "Eclipse reoptimized"

plans, respectively. Similarly, the Rectum V59Gy values were 5.0%, 5.0%, 4.7%, 4.9%, and 4.8% for the same plans, respectively.

In summary, the Ethos IOE system consistently produced VMAT plans with higher doses compared to IMRT plans. The Ethos treatment planning system (TPS) took an average of 13 minutes to generate 2-full arc VMAT plans, while 12-field IMRT plans took around 5 minutes. The efficiency of the Varian Ethos TPS allows for the generation of multiple treatment plans within a reasonable timeframe, and the quality of these plans can be considered clinically acceptable when compared to manually created treatment plans.

CHAPTER III

RESEARCH METHODOLOGY

3.1 **Research design**

This study is a retrospective study, by collecting the data of patients with prostate cancer who underwent treatment on the Ethos at King Chulalongkorn Memorial Hospital (KCMH).

3.2 **Research design model**

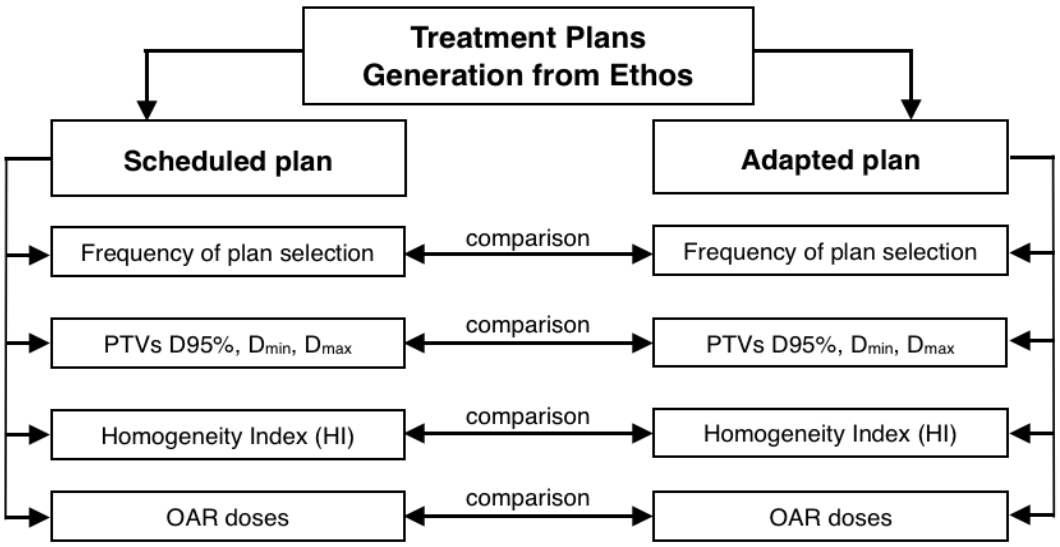


Figure 3.1 Research design model.

3.3 **Conceptual framework**

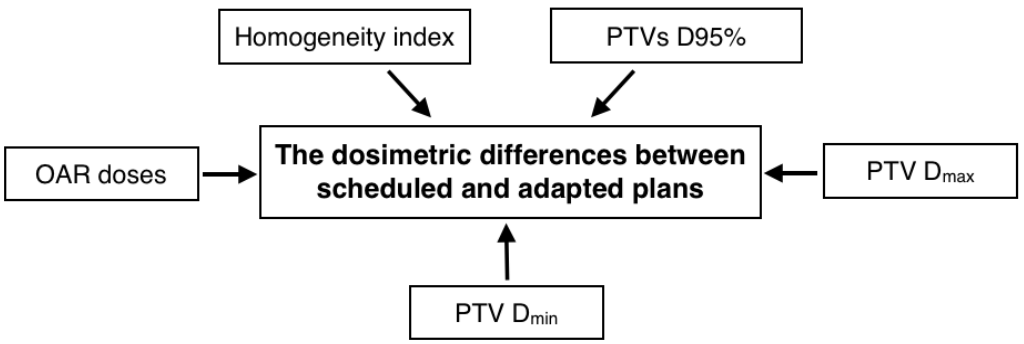


Figure 3.2 Conceptual framework.

3.4 **Key Word**

Adaptive radiotherapy, Ethos, dosimetric differences, prostate cancer radiotherapy

3.5 **The sample**

3.5.1 Target population

Dose volume histogram of prostate cancer patients who had previously been treated on Ethos daily adaptive radiotherapy at KCMH.

3.5.2 Sample population

Dose volume histogram of prostate cancer patients who had previously been treated on Ethos daily adaptive radiotherapy at KCMH that met the eligible criteria.

3.5.3 Eligible criteria

3.5.3.1 The inclusion criteria

Male patients with prostate cancer who had radiation only prostate (without nodal involvement) with hypofractionated treatment of 60 Gy in 20 fractions and treated with adaptive treatment.

3.5.3.2 The exclusion criteria

Patients who did not complete the treatment course.

3.5.4 Sample size determination

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \sigma^2}{d^2}$$

Significance level (α): p = 0.05 ($Z_{0.975}$ = 1.96)
Statistical power (1-β): 90% power ($Z_{0.9}$ = 1.28)
Difference of mean (d): μ_1-μ_2 = 2.9
Variability (Standard Deviation) = 5.3

The difference of mean and the variability are the data from Moazzezi M et al.[11], which resulted that adaptation improved CTV

D98% by 2.9 ± 5.3%. This study used all available data of prostate cancer patients at KCMH. From the calculation, n is equal to 36. So, 100 fractions of 5 patients who had undergone the Ethos treatment at KCMH is acceptable as a sample size for this study.

3.6 **Materials**

3.6.1 Ethos™ therapy system (Varian Medical System, Palo Alto, CA)

The Ethos machine is a linear accelerator that is mounted on a ring and equipped with a 6 MV FFF beam. It incorporates an online adaptive radiation therapy workflow that relies on high-quality iterative cone-beam CT images. The machine features a dual-layer multileaf collimator (MLC) design, with 29 leaf pairs in the proximal MLC leaf bank and 28 leaf pairs in the distal MLC leaf bank. The leaf banks are positioned at a half-leaf interval, resulting in an effective leaf width of 5.0 mm while minimizing interleaf leakage. The machine has a maximum square field size of 28x28 cm^2, and it also offers extended field capability in the longitudinal direction, with a shift of 8 cm.[13, 14]

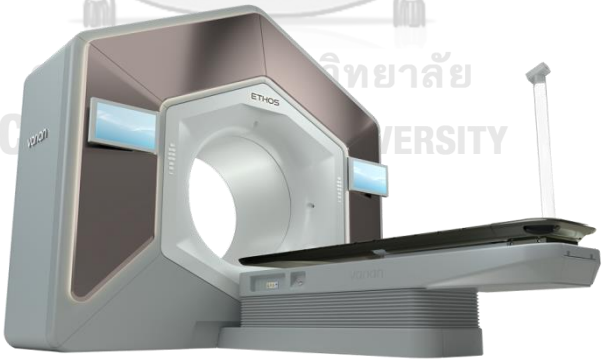


Figure 3.3 Ethos™ therapy system.

3.6.2 Ethos treatment planning version 1.1

It has two main functions, including auto segmentation and optimization. It applies an AI-algorithm based on convolutional neural networks for the detection of daily anatomy. Ethos generates a simulated CT by deformable registering the planning CT into the

daily CBCT geometry. Hounsfield units (HU) from this simulated CT are related to electron density information that is used for dose calculation.

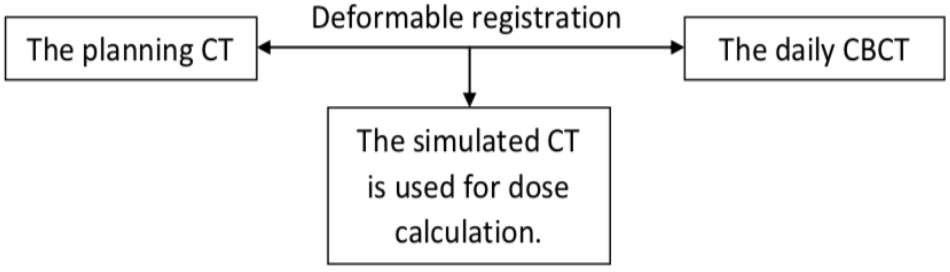
3.6.3 ArcCHECK®

The AAPM Task Group 218 recommends the use of a specific phantom for fulfilling 3D measurement requirements. This phantom, made of PMMA (acrylic), is designed to be water-equivalent. It has a cylindrical shape and features a three-dimensional array of 1,386 diode detectors arranged in a spiral pattern. These detectors have a resolution of 0.8x0.8 mm and are spaced 10 mm apart. The purpose of this phantom is to measure and correlate various parameters such as gantry angle, leaf-end position, absolute dose, and time. By doing so, it helps identify any potential sources of error throughout the patient volume.

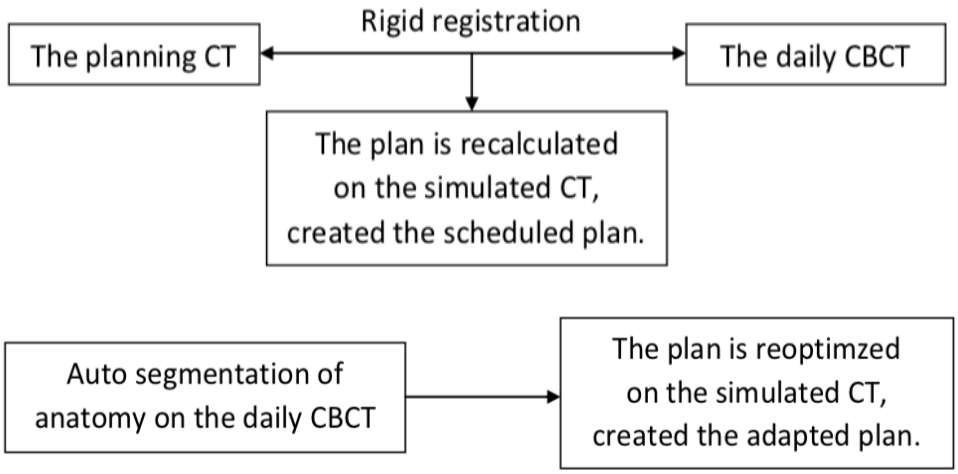
3.7 **Methods**

3.7.1 Ethos plans generation

In order to generate the scheduled and adapted plans, Ethos uses simulated CT images for dose calculation. This simulated CT images are generated by deformably image registering the planning CT to the daily kV-CBCT using the commercial B-spline deformation model, Velocity™.



For the scheduled plan generation, the original treatment plan applies the automated match, then is recalculated based on the anatomy of the day. The rigid registration process includes the treatment isocenter matching and the target volumes matching.



3.7.2 Treatment data collection from Ethos

The treatment data of 5 patients in total of 100 treatment fractions with prostate cancer who had previously been treated with volumetric modulated arc therapy technique on Ethos daily adaptive radiotherapy at KCMH were collected. The treatment data in each fraction of both scheduled and adapted plans including PTVs D95%, D_{min}, D_{max}, OAR doses, frequency of plan selection, and homogeneity index, were compared.

In the context of hypofractionated treatment planning for prostate cancer (specifically, delivering 60 Gy of radiation in 20 fractions), the term PTV D95% refers to the minimum dose received by 95% of the Planning Target Volume (PTV). This definition is based on the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) protocol.[15] randomized controlled trial, the PTVs consist of PTV1, PTV2, and PTV3 which has dose constraints at 48 Gy, 57.6 Gy, and 60 Gy, respectively. For rectal dose, a new panel of dose constraints for hypofractionated schedules to 60 Gy are V20Gy <85%, V30Gy <57%, V40Gy <38%, V50Gy <22%, and V60Gy <0.01%. For bladder dose, dose constraints are V40.8Gy <50%, V48.6Gy <25%, and V60Gy <5%.

Outlining of PTVs contour based on CHHiP protocol; PTV3 = prostate + 5mm, except to rectum where 0 mm. PTV2 = prostate + 10 mm, except to rectum where 5 mm. PTV1 = prostate + seminal vesicles + 10 mm.

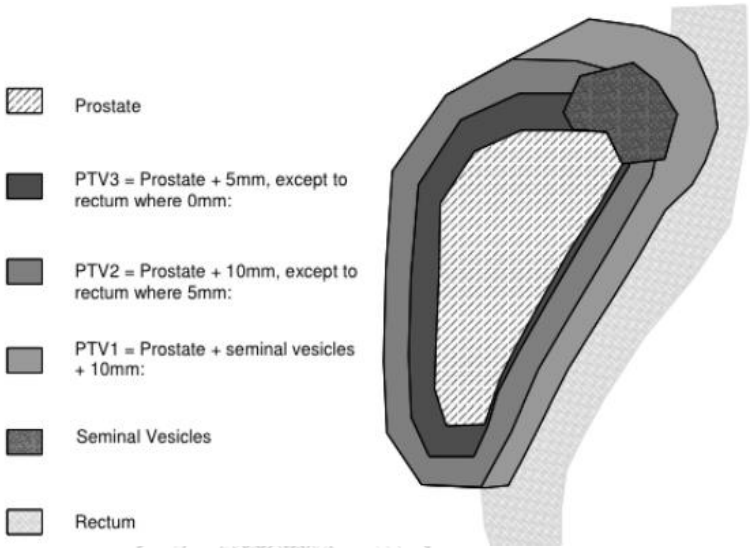


Figure 3.4 Outlining of PTVs contour based on CHHiP protocol.

3.7.3 Homogeneity index calculation

Homogeneity index is an objective tool to analyze the uniformity of dose distribution in the target volume**.**

$$Homogeneity\ index = \frac{D2\% - D98\%}{D_p}$$

D2% = Minimum dose to 2% of the target volume
D98% = Minimum dose to 98% of the target volume
D_p = Prescribed dose

This formula is widely used in literature as it offers a common approach. The selection of D98% and D2% to represent the

minimum and maximum dose is based on the sensitivity of true minimum or maximum dose calculations to factors like grid size and placement, as well as the presence of high dose gradients in IMRT. As a result, directly calculating the true minimum or maximum dose may not be reliable. Instead, choosing the maximum or minimum dose within a volume (such as D2% or D9%8) is preferred. Therefore, all these definitions of homogeneity index (HI) essentially express the ratio between the maximum and minimum dose within the target volume, with a lower value indicating a more homogeneous dose distribution within that volume.[16, 17]

3.8 **Statistical analysis**

The dosimetry data including PTVs D95%, D_{min}, D_{max}, OAR doses, and homogeneity index were compared as Mean and Standard Deviation (S.D.) between the scheduled and adapted plans. The frequency of plan selection is calculated as the percentage of fractions. The data was analyzed using paired t-test when the null hypothesis (H_0): there is no difference between the adapted and scheduled plans, where *p*-value less than 0.05 was considered statistically significant.

3.9 **Ethical consideration**

Since the dosimetric volume histogram data were collected from patients, this study was submitted and approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No. 0461/65).

CHAPTER IV

RESULTS

4.1 **Patient-specific QA**

All the plans and calculated doses were exported from Ethos system to display in Eclipse. The average gamma passing rate with the criteria of 3% dose difference and 2 mm distance to agreement from all 5 plans was 98.1±1.1% as presented in Table 4.1.

Table 4.1 Results of Ethos patient specific VMAT QA.

Patient no.	Gamma passing rate (%)
1	98.8
2	96.3
3	98.7
4	98.0
5	99.0
average	98.1±1.1

4.2 **D95% of PTVs**

The D95% of PTV1, PTV2, and PTV3 were compared between scheduled and adapted plans. For PTV3 D95%, the adapted plan had values closer to the reference plan dose from the original plan on CT simulation images than the scheduled plan for 63 of 100 fractions, 73 fractions for PTV2 D95% and 61 fractions for PTV1 D95%. There were 15 fractions that values of D95% from both plans were equal in PTV3, 6 fractions in PTV2 and 9 fractions in PTV1. The adapted plan had D95% values higher than the reference plan of 0.05% for PTV1 and 0.47% for PTV3. For the

scheduled plan, D95% values were 0.18% lower than the reference plan for PTV1, 3.60% for PTV2 and 2.14% for PTV3.

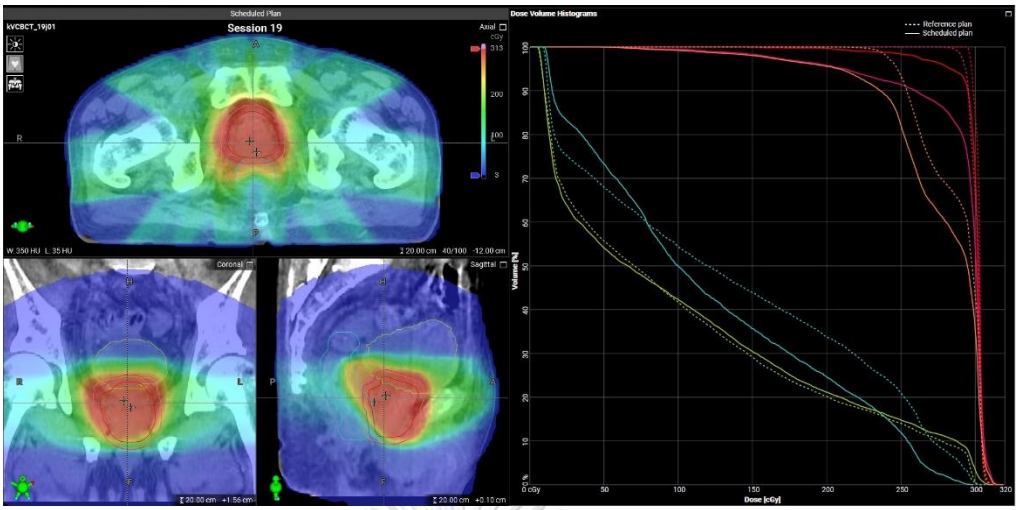
On average of all patients, table 4.2 shows that PTV2 D95% and PTV1 D95% of the adapted plan were significantly higher than the scheduled plan with less variation. However, adaptation pushed the average dose per fraction of PTV2 D95% and PTV1 D95% above the dose constraints.

Table 4.2 Comparison of PTVs D95% between the scheduled and adapted plans.

D95%	**Dose constraints for 1 fraction (cGy)**	**Average dose per fraction of scheduled plan (cGy)**	**Average dose per fraction of adapted plan (cGy)**	**Average of percentage difference between two plans in each fraction**	***p*-value**
PTV1	240	245.7 ± 14.6	252.2 ± 6.4	2.7%	<0.001
PTV2	288	280.2 ± 15.1	289.0 ± 5.6	3.2%	<0.001
PTV3	300	298.7 ± 5.3	299.4 ± 3.1	0.2%	0.144

As an example, the DVH of patient 1 in figure 4.1 shows that PTVs D95% in the scheduled plan were much lesser than the values in the reference plan but the adapted plan pushed the values closer to the reference plan.

a)



b)

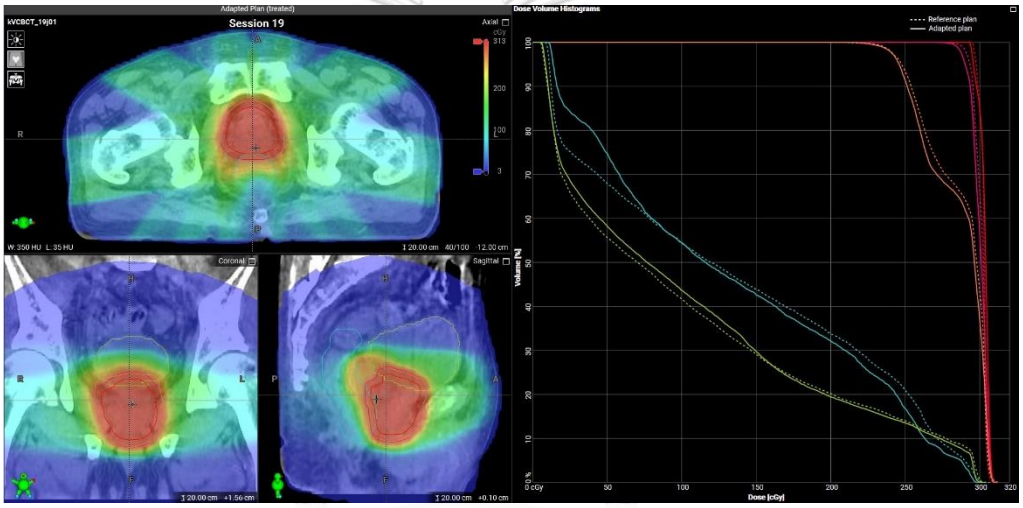


Figure 4.1 Comparison of DVH metrics for the scheduled plan (a) versus adapted plan (b) of patient number 1 in a representative fraction where PTV3 dose is in red, PTV2 is in purple, PTV1 is in pink, rectal dose is in blue, and bladder dose is in green.

4.3 **D95% of PTV3**

If compared with the scheduled plan**,** the adapted plan produced better results of PTV3 D95% in which the total dose and average dose per fraction were closer to the reference plan in all five patients, shown in table 4.3. However, for patient 3 and patient 5, the total doses were less than the dose constraints in the scheduled plan but the adapted plan pushed the value above the dose constraints.

Table 4.3 Comparison of PTV3 D95% between the scheduled and adapted plans.

Patient no.	Dose constraint for 20 fractions (cGy)	Reference plan		Scheduled plan		Adapted plan	
		Total dose (cGy)	Dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)
1	6000	5953	298	5909	295.5 ± 3.3	5924	296.2 ± 0.7
2		5917	296	5891	294.6 ± 1.5	5920	296.0 ± 0.3
3		6006	301	5966	298.3 ± 1.8	6036	301.8 ± 1.4
4		5992	300	6142	307.1 ± 4.4	6033	301.7 ± 2.7
5		6020	301	5959	298.0 ± 2.4	6022	301.1 ± 1.3

The example of patient number 5 that had PTV3 D95% of the adapted plan closer to the reference plan dose than the scheduled plan is shown in Figure 4.1. The average of PTV3 D95% of this patient was 296.0 ± 0.3 cGy and 294.5 ± 1.5 cGy for adapted and scheduled plans respectively. Adaptation produced the exact values of PTV3 D95% as planned for 98% of fractions.

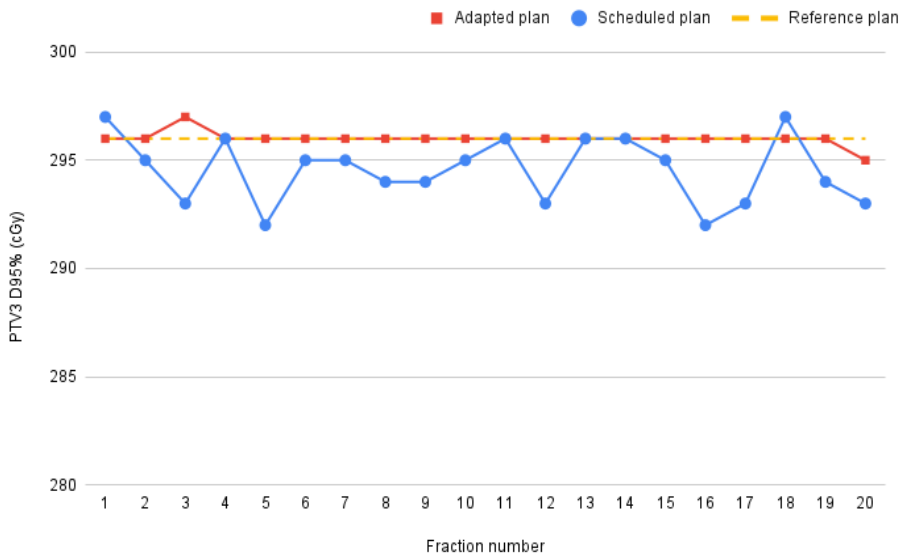


Figure 4.2 Comparison of PTV3 D95% values for the scheduled plan versus adapted plan of patient number 5 in 20 fractions.

4.4 **D95% of PTV2**

For every patient, the adapted plan produced closer values to the reference plan more than the scheduled plan with less variation, shown in table 4.4. For patient 4, the scheduled plan had the total dose and average dose per fraction higher than the reference plan, but the adapted plan could lower it to be closer to the reference plan. Even though the total dose of the adapted plan was closer to the reference plan, most of the values exceeded dose constraints, while the total dose of the scheduled plan was more likely to be within the dose constraint.

Table 4.4 Comparison of PTV2 D95% between the scheduled and adapted plans.

Patient no.	Dose constraint for 20 fractions (cGy)	Reference plan		Scheduled plan		Adapted plan	
		Total dose (cGy)	Dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)
1	5760	5868	293	5433	271.7±16.2	5827	291.4 ± 1.2
2		5823	291	5531	276.6 ± 6.4	5818	290.9 ± 1.5
3		5804	290	5790	289.5 ± 2.2	5816	290.8 ± 1.0
4		5793	290	5942	297.1 ± 5.7	5788	289.4 ± 2.1
5		5760	288	5319	266.0 ± 12.0	5652	282.6 ± 9.9

4.5 **D95% of PTV1**

Table 4.5 Comparison of PTV1 D95% between the scheduled and adapted plans.

Patient no.	Dose constraint for 20 fractions (cGy)	Reference plan		Scheduled plan		Adapted plan	
		Total dose (cGy)	Dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)
1	4800	4951	248	4779	239.0 ± 9.5	4977	248.9 ± 2.6
2		4976	249	4686	234.3 ± 18.0	5022	251.1 ± 3.8
3		5135	257	5178	258.9 ± 2.8	5148	257.4 ± 3.0
4		5120	256	5166	258.3 ± 5.1	5147	257.4 ± 4.0
5		4920	246	4764	238.3 ± 8.6	4923	246.2 ± 7.7

Same with PTV3 and PTV2, the adapted plan produced higher PTV1 D95% and closer values to the reference plan than the scheduled plan in every patient, shown in table 4.5. If the dose was high in the scheduled plan, the adapted plan could lower it to nearer the reference plan. If the dose was low in the scheduled plan, the adapted plan pushed the dose to even higher than the reference plan. However, the total dose from reference and adapted plans were higher than dose constraint in every patient, except some scheduled plans that could produce the values within the dose constraint.

4.6 D_{min} of PTV3

Table 4.6 Comparison of D_{min} of PTV3 between the scheduled and adapted plans.

Patient no.	Dose constraint for 20 fractions	Reference plan		Scheduled plan		Adapted plan	
		Total dose (cGy)	Dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)
1	≥ 5700 cGy (95% of 6000 cGy)	5920	296	5472	273.6 ± 32.6	5866	293.3 ± 1.2
2		5880	294	5646	282.3 ± 7.6	5825	291.3 ± 1.0
3		5940	297	5764	288.2 ± 4.2	5827	291.4 ± 2.1
4		5980	299	5790	289.5 ± 7.8	5843	292.2 ± 2.0
5		5940	297	5152	257.6 ± 27.1	5768	288.4 ± 9.1

D_{min} defines as the minimum dose to 99% of the volume within the PTV. In every patient, the adapted plan had higher values of PTV3 D_{min} than the scheduled plan in both the total dose and average dose per fraction, shown in table 4.6. Overall, the adapted plan produced better results, in which the total dose was higher than 5700 cGy as recommended by CHHiP, while some scheduled plans had the values below the dose constraint. On average, the adapted plan had PTV3 D_{min} equal to 291.3 ± 4.6 cGy and 278.2 ± 22.6 cGy for the scheduled plan. The adapted plan produced higher PTV3 D_{min} than the scheduled plan for 4.9 ± 4.7% with *p*-value less than 0.001.

4.7 D_{max} of PTV3

Table 4.7 Comparison of D_{max} of PTV3 between the scheduled and adapted plans.

Patient no.	Dose constraint for 20 fractions	Reference plan		Scheduled plan		Adapted plan	
		Total dose (cGy)	Dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)	Total dose (cGy)	Average dose per fraction (cGy)
1	≤ 6300 cGy (105% of 6000 cGy)	6140	307	6210	310.5 ± 2.7	6149	307.5 ± 0.9
2		6160	308	6162	308.1 ± 1.6	6154	307.7 ± 0.9
3		6480	324	6434	321.7 ± 1.3	6583	329.2 ± 2.4
4		6500	325	6754	337.7 ± 5.5	6618	330.9 ± 3.5
5		6220	311	6240	312.0 ± 1.5	6211	310.6 ± 0.8

D_{max} defines as the maximum dose to 1% of the volume within the PTV. From the recommendation, PTV3 D_{max} should be equal to or less than 6300 cGy. As shown in table 4.7, for patient 3 and 4, the total dose was higher than dose constraint in both scheduled and adapted plans. In patient 3, the adaptation pushed the values to even higher. On average, the adapted plan had PTV3 D_{max} equal to 317.2 ± 10.8 cGy and 318.0 ± 11.3 cGy for the scheduled plan. Overall, the adapted plan produced lower PTV3 D_{max} than the scheduled plan for 0.3% ± 1.6% with *p*-value equal to 0.149.

4.8 Homogeneity index

For homogeneity index (HI), the ideal value is equal to zero and increases as homogeneity decreases. On average of 5 patients, the HI of PTV3 of the adapted plan and scheduled plan was 0.06 ± 0.03 and 0.07 ± 0.03, respectively. The average HI of the adapted plan was less than the scheduled plan for 16.2% ± 21.6% (*p*-value <0.001). Patient 1, 2, 4, and 5 had the average HI from the adapted plan lower than the scheduled plan for 27.19%, 16.94%, 8.74%, and 43.10% respectively (*p*-value <0.001). However, there was only patient 3 that had the average HI from the adapted

plan less than the scheduled plan for 14.98% (*p*-value <0.001) in 99% of fractions as shown in figure 5.2

4.9 **Bladder dose**

Table 4.8 Comparison of bladder dose between the scheduled and adapted plans.

Parameters	Bladder constraints (%Vol)	Reference plan (%Vol)	Scheduled plan (%Vol)	Adapted plan (%Vol)	Average of diff. between two plans (%)	*p*-value
V4080 cGy	50%	12.5%	23.3%	20.6%	0.1%	<0.001
V4860 cGy	25%	9.2%	16.6%	14.4%	0.1%	<0.001
V6000 cGy	5%	1.1%	3.9%	2.2%	0.7%	<0.001

For bladder dose, there were 23 fractions that had values of V60Gy exceeding the threshold, adaptation could lower the values for 0.7 ± 0.6% on average (*p*-value <0.001). For V40.8Gy and V48.6Gy, the adapted plan lowered the values to 0.1 ± 0.2% and 0.1 ± 0.2% respectively (*p*-value <0.001). Overall, the adapted plan had the values less than the scheduled plan and both plans produced values below bladder constraints. From a representative patient shown in figure 4.1, the bladder doses from V40-60Gy were slightly higher than the reference plan in the scheduled plan but the adapted plan lowered some of the values lesser than the reference plan.

4.10 **Rectal dose**

Table 4.9 Comparison of rectal dose between the scheduled and adapted plans.

Parameters	Rectal constraints (%Vol)	Reference plan (%Vol)	Scheduled plan (%Vol)	Adapted plan (%Vol)	Average of diff. between two plans (%)	*p*-value
V2000 cGy	85%	64.8%	71.7%	69.8%	1.5%	0.047
V3000 cGy	57%	47.2%	52.4%	47.9%	4.8%	0.001
V4000 cGy	38%	32.8%	37.3%	33.5%	5.7%	0.001
V5000 cGy	22%	17.6%	22.3%	18.1%	12.1%	<0.001
V6000 cGy	0.01%	0.2%	3.5%	0.6%	12.5%	<0.001

Adaptation could reduce rectal dose V20, V30, V40, V50, and V60 Gy for 1.47%, 4.83%, 5.70%, 12.09%, and 12.52%, respectively. Especially for V50Gy that the value was higher than the rectal constraint in the scheduled plan but the adapted plan could lower it to within tolerance. There were more differences between two plans when the percentage of volume was higher. However, for V60Gy both plans had the values exceeded rectal constraint. As shown in figure 4.1 that V20Gy to V60Gy of both scheduled and adapted plans were lower than values in the reference plan as values of adapted plan were closer to the reference plan than the scheduled plan.

4.11 **Frequency of plan selection**

The adapted plan was selected for treatment by radiation oncologists in 98% of 100 fractions. Both fractions that the scheduled plan was selected for treatment, were from patient 3. In general, the adapted plan was often selected because it was superior to the scheduled plan in terms of higher target volume dose and better sparing dose to OARs.

CHAPTER V

DISCUSSION AND CONCLUSION

5.1 **Discussion**

In this study, we provided evidence of the efficiency of adaptive radiotherapy for prostate cancer patients by investigating the dosimetric differences between the scheduled and adapted plans generated from Ethos. We firstly performed patient-specific QA for all the plans in which every plan passed the gamma passing rate that was ≥ 95% for the criteria of a dose difference of 3% and a distance to agreement of 2 mm with 10% threshold based on AAPM Task Group 218. Our results showed that the adapted plan produced PTVs D95% closer to the reference plan for 66% of fractions and the same values from both plans for 10% of fractions, where the adapted plan was selected for treatment in 98% of fractions. Similar to the results from Byrne M et al.[10] which found that the adaptive plan met more goals than the scheduled plan in 78% of fractions and in 15% of fractions the number of goals met was the same, where the adapted plan was selected for treatment in 95% of fractions. For PTVs D95%, the adaptation usually produced values higher and closer to the reference plan than the scheduled plan. There were 79% of fractions that the adapted plan had higher PTV3 D95% for 0.2 ± 1.2% on average than the scheduled plan in our study. The results from Moazzezi M et al.[11] showed that adaptation produced higher CTV doses for 92.5% of 240 fractions with a difference of 2.9 ± 5.3% on average. The lesser percentage of fractions that the adapted plan produced higher results in our study might be due to the variety of inclusion criteria for selecting patients to treat with Ethos and the difference in clinical treatment goals based on each hospital. However, if the dose was less in the scheduled plan, the adapted plan often pushed it above dose constraints. This showed significant related evidence that the adapted plan could help to increase CTV and PTV doses to more than 50% of fractions and could raise the dose from lower than the reference plan to closer or higher the reference plan for a better target dose. On the other hand, this in turn would lead to creating some hot areas in target volume. However, oncologists usually prefer the overdose to the target volume

rather than the under dose, so the adapted plan usually was selected for treatment over 98% of fractions.

For PTV3 D_{min}, the adaptation could improve the dose very well in every patient if compared to the scheduled plan, where there was one fraction that the difference between the two plans reached to 66.4%. For PTV3 D_{max}, the adapted plan also improved the results by decreasing the dose effectively in every patient. On the contrary, in patient 3, the adapted plan failed to decrease the dose and produced higher values than the scheduled plan in every fraction shown in figure 5.1. This was related to the HI in which the formula was calculated from D_{max}, which made the HI of patient 3 in the adapted plan higher than the scheduled plan in 19 of 20 fractions shown in figure 5.2. It was unlikely for other patients that the adaptation could improve the homogeneity very well. However, even less homogeneity was produced from the adapted plan, it still was selected over the scheduled plan for 18 of 20 fractions in patient 3 due to the higher dose of PTV D95% and lower dose to OARs.

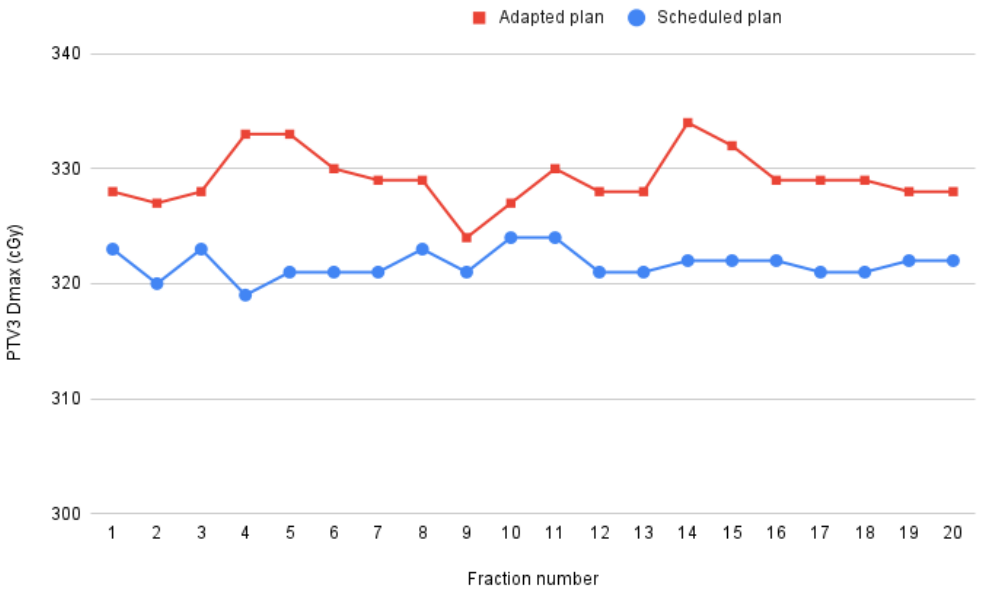


Figure 5.1 Comparison of PTV3 D_{max} for the adapted versus scheduled plans of patient number 3 in 20 fractions.

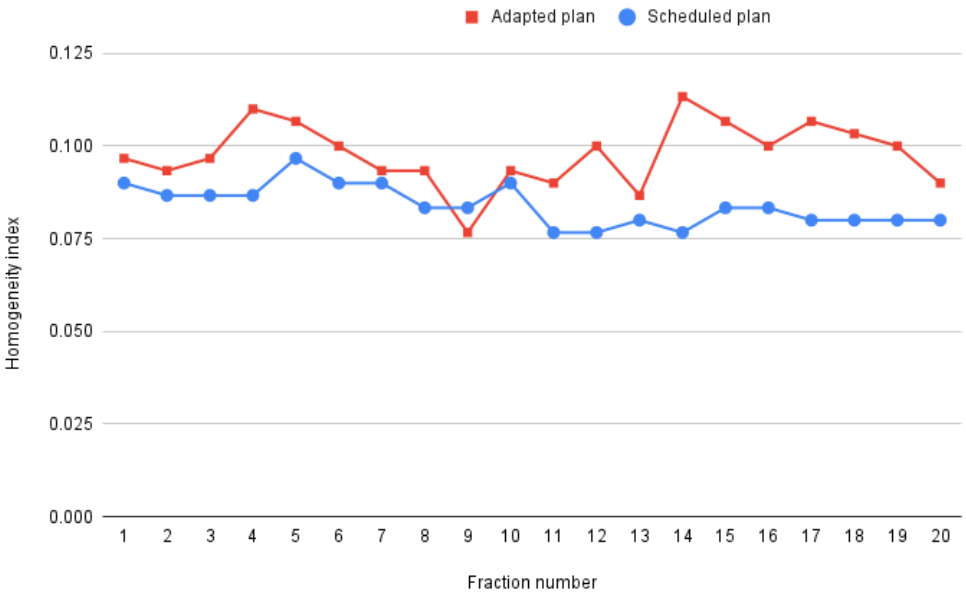
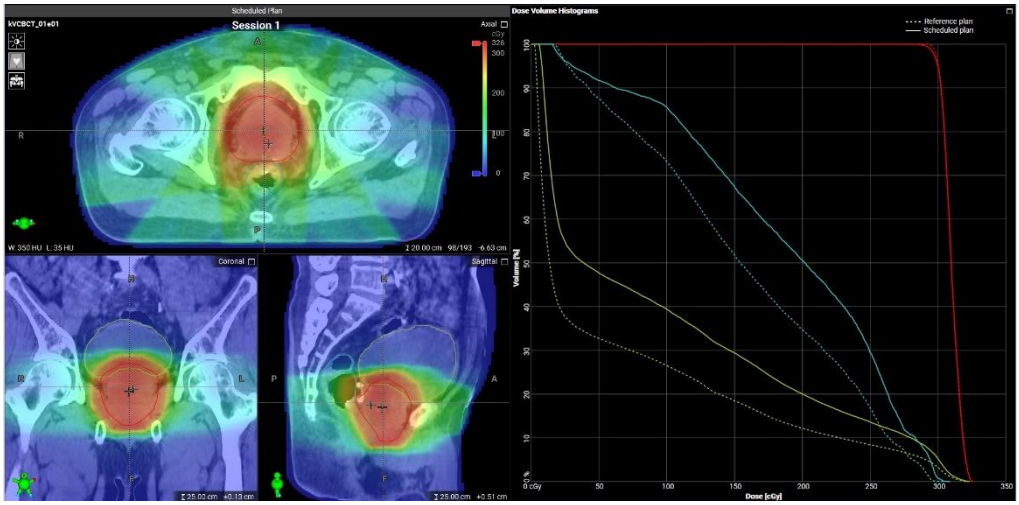


Figure 5.2 Comparison of homogeneity index for the adapted versus scheduled plans of patient number 3 in 20 fractions.

As an example, figure 5.3 shows the DVH metrics of patient number 3 in a representative fraction. Even though the adapted plan could lower bladder and rectal dose closer to the reference plan than the scheduled plan, the adaptation also pushed PTV3 dose higher than the reference plan. The reason that PTV doses from the scheduled plan never get higher than the reference plan is because of the error of the tumor movement or setup error on each day of treatment.

a)



b)

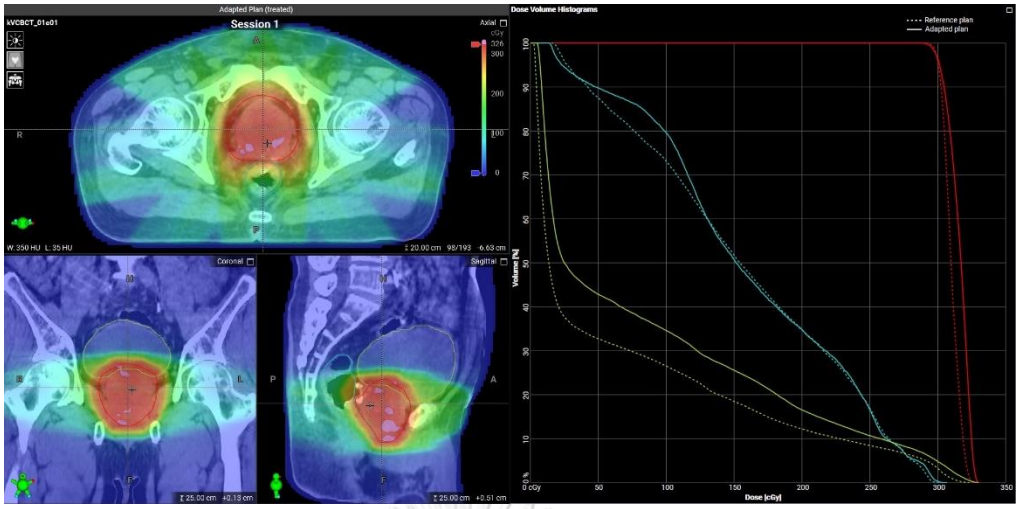


Figure 5.3 Comparison of DVH metrics for the scheduled plan (a) versus adapted plan (b) of patient number 3 in a representative fraction where PTV3 dose is in red, rectal dose is in blue, and bladder dose is in green.

For OARs doses which include bladder and rectum, in overall, adaptation also produced better results than the scheduled plan. For bladder dose, the adaptation had the values significantly lower than the scheduled plan. The results were in the same direction with the study of Moazzezi M et al.[11] in which the adaptation improved OAR sparing 13.1% for bladder V90%, and improved OAR sparing 6.5% for rectum V90%. In contrast with other patients, in patient 5, it was observed that the adapted plan had more percentage of rectal volume that received the same amount of dose with the scheduled plan shown in table 5.1. However, the adapted plan still was selected for treatment in 100% of 20 fractions because the percentage that received each dose did not exceed the rectal constraints.

Table 5.1 Comparison of rectal dose between the scheduled and adapted plans of a representative patient number 5.

Parameters	Rectal constraints (%Vol)	Scheduled plan (%Vol)	Scheduled plan (%Vol)	Adapted plan (%Vol)
V2000 cGy	85%	78.2%	66.7% ± 3.5%	76.0% ± 6.6%
V3000 cGy	57%	50.5%	42.0% ± 4.5%	52.4% ± 4.5%
V4000 cGy	38%	35.4%	28.4% ± 3.9%	35.9% ± 2.6%
V5000 cGy	22%	19.5%	14.5% ± 3.3%	17.6% ± 1.9%
V6000 cGy	0.01%	0.0%	0.1% ± 0.4%	0.2% ± 0.2%

One of the limitations of this retrospective study was the small sample size due to the available data of the current number of patients in KCMH. Even though the higher dose of PTVs was improved by the adaptation, the dose at OARs still needed to be observed because the adapted plan could also push the values of OARs higher than the scheduled plan in some cases as our example. For further studies, the homogeneity index could be one factor that should be continued to study, as shown in one representative patient that the scheduled plan produced better results over the adapted plan in almost every fractions.

5.2 **Conclusion**

The adapted plan produces better results and less variation in PTV doses, and also better in HI, and OAR doses, where it pushes the average of D_{min} higher and lower the average of D_{max}, HI, and OAR doses. This shows significant improvements by the adaptation from Ethos. In comparison with the scheduled plan, the adapted plan produces PTVs D95% closer to the reference plan for 66% of fractions. However, the higher dose of adapted plan over the reference plan may lead to creating some hot areas in target volume. Thus, a careful review by oncologists is required prior to dose delivery.

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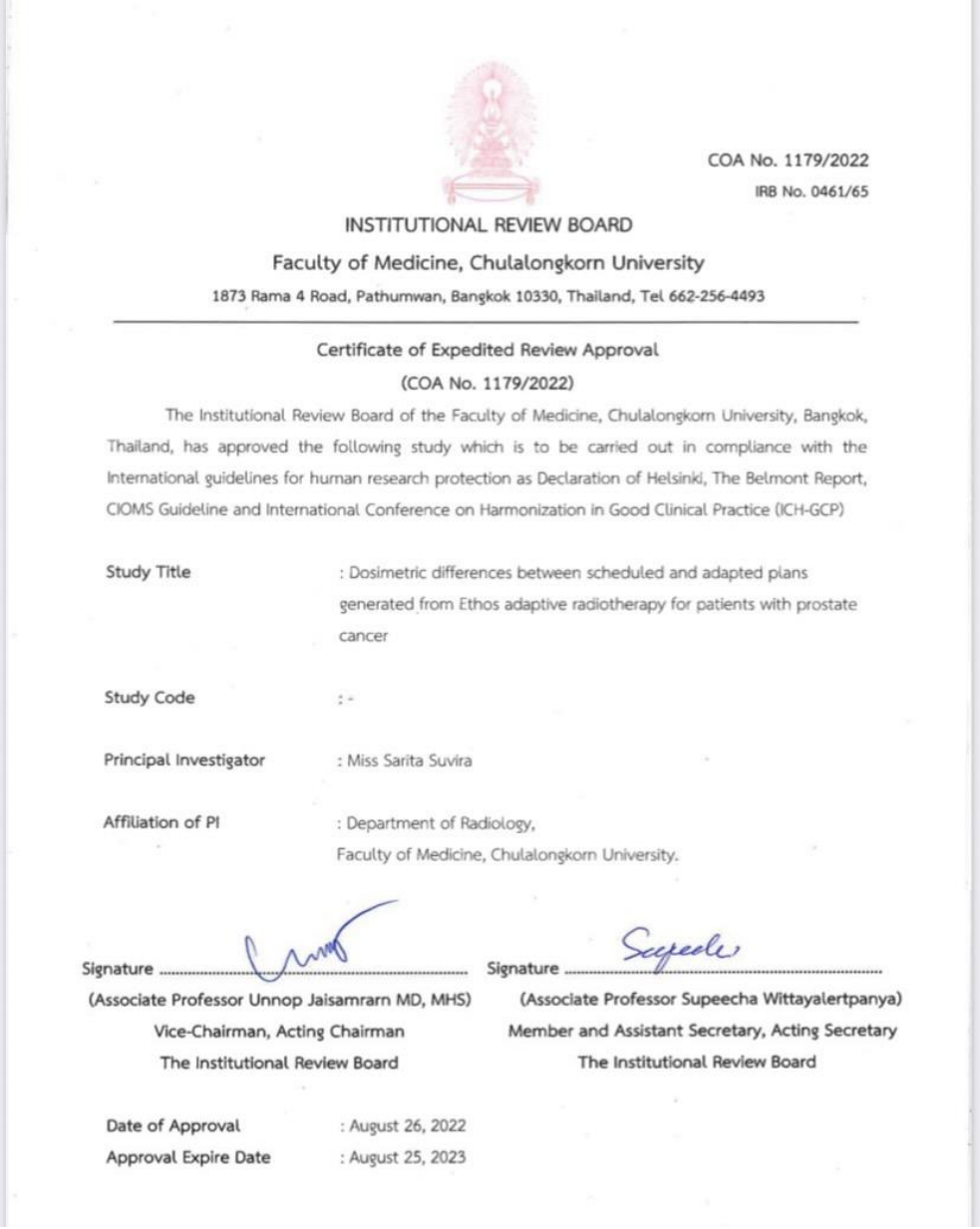
APPENDIX

The approval of institutional review board

Certificate approval from institutional review board (IRB) of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.



COA No. 1179/2022
IRB No. 0461/65

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Pathumwan, Bangkok 10330, Thailand, Tel 662-256-4493

Certificate of Expedited Review Approval
(COA No. 1179/2022)

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : Dosimetric differences between scheduled and adapted plans generated from Ethos adaptive radiotherapy for patients with prostate cancer

Study Code : -

Principal Investigator : Miss Sarita Suvira

Affiliation of PI : Department of Radiology, Faculty of Medicine, Chulalongkorn University.

Signature ..... Signature .....
(Associate Professor Unnop Jaisamrarn MD, MHS) (Associate Professor Supeecha Wittayalertpanya)
Vice-Chairman, Acting Chairman Member and Assistant Secretary, Acting Secretary
The Institutional Review Board The Institutional Review Board

Date of Approval : August 26, 2022
Approval Expire Date : August 25, 2023

Figure A The approval of institutional review board.

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