Dosimetric comparison between using daily cone beam CT and planning CT in volumetric modulated arc therapy technique for prostate cancer therapy

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การเปรียบเทียบปริมาณรังสีระหว่างการใช้ภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยประจำวันและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษา ในเทคนิคการฉายรังสีแบบปรับความเข้มหมุนรอบตัวผู้ป่วย สำหรับผู้ป่วยมะเร็งต่อมลูกหมาก

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จุฬาลักษณ์ ชนะโยธา : การเปรียบเทียบปริมาณรังสีระหว่างการใช้ภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยประจำวันและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษา ในเทคนิคการฉายรังสีแบบปรับความเข้มหมุนรอบตัวผู้ป่วย สำหรับผู้ป่วยมะเร็งต่อมลูกหมาก. (Dosimetric comparison between using daily cone beam CT and planning CT in volumetric modulated arc therapy technique for prostate cancer therapy) อ.ที่ปรึกษาหลัก : ดร.ทวีป แสงแห่งธรรม

ความแปรปรวนของรูปร่างและขนาดของอวัยวะภายในร่างกาย โดยเฉพาะกระเพาะปัสสาวะและลำไส้ตรงของผู้ป่วยมะเร็งต่อมลูกหมากเป็นปัจจัยหลักที่อาจส่งผลกระทบต่อการควบคุมโรค และก่อให้เกิดอันตรายต่อเนื้อเยื่อปกติข้างเคียงในการรักษาผู้ป่วยด้วยการฉายรังสี วัตถุประสงค์ของการศึกษานี้ เพื่อตรวจสอบความแตกต่างของปริมาณรังสีด้วยการใช้ภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยประจำวันและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษาในผู้ป่วยมะเร็งต่อมลูกหมากที่รักษาด้วยเทคนิคการฉายรังสีแบบปรับความเข้มหมุนรอบตัวผู้ป่วย โดยทำการเปรียบเทียบค่า Hounsfield unit กับ electron density ในหุ่นจำลอง Catphan® 600 ระหว่างภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษา จากนั้นทำการตรวจสอบความถูกต้องของโปรแกรมวางแผนการรักษา โดยคำนวณปริมาณรังสีบนภาพ Anthropomorphic RANDO® จากการสแกนเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยและเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษา จากนั้นแผนการรักษาตั้งต้นของผู้ป่วยตัวอย่างจะถูกส่งไปยังภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษา และส่งแผนการรักษาที่ได้จากภาพทั้งสองไปยังโปรแกรม Sun Nuclear Patient เพื่อทำการเปรียบเทียบในเทอมของ Gamma index และทำการตรวจสอบระบบการลงทะเบียนภาพระหว่างภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษา โดยทำการลงทะเบียนภาพ และเลื่อนแฟนทอมไปที่ระยะต่างๆ ทำการเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยและลงทะเบียนภาพซ้ำอีกครั้ง อ่านค่าความคลาดเคลื่อนที่เกิดขึ้น จากนั้นทำการตรวจสอบปริมาณรังสีทางคลินิก โดยใช้ 299 ชุดข้อมูลภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยประจำวัน จากผู้ป่วยมะเร็งต่อมลูกหมากทั้งหมด 7 ราย ใช้ลำรังสีโฟตอน 6 ล้านโวลต์ กำหนดปริมาณรังสีที่ผู้ป่วยได้รับที่ 79.2 เกรย์ ในการฉายรังสี 44 ครั้ง นำชุดข้อมูลภาพมาทำการกำหนดขอบเขตการรักษาดังนี้ ต่อมลูกหมากรวมกับถุงสร้างสารบำรุงตัวอสุจิ (Clinical Target Volume: CTV) และกำหนดขอบเขตที่ขยายจาก CTV ไป 8 มิลลิเมตรในทุกทิศทาง ยกเว้นด้านหลังที่ขยาย 5 มิลลิเมตร (Planning Target Volume: PTV) ตามรายงานวิจัย RTOG 0815 รวมไปถึงการกำหนดขอบเขตของกระเพาะปัสสาวะและลำไส้ตรงของผู้ป่วยในแต่ละวัน แผนการรักษาตั้งต้นของผู้ป่วยแต่ละรายจะถูกส่งไปยังภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยประจำวัน และคำนวณการรักษาอีกครั้งด้วยโปรแกรม Eclipse™ จากนั้นทำการเปรียบเทียบปริมาณรังสีระหว่างการใช้ภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยประจำวันและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษาที่ปริมาตรของ CTV ที่ได้รับปริมาณรังสีที่ 100% ของปริมาณรังสีที่กำหนด ปริมาตรของ PTV ที่ได้รับปริมาณรังสีที่ 95% ของปริมาณรังสีที่กำหนด และปริมาตรของกระเพาะปัสสาวะและลำไส้ตรงที่ได้รับปริมาณรังสีที่ 75, 70, 65 และ 60 เกรย์ ผลการศึกษาพบว่าค่าความแตกต่างของ Hounsfield unit ในแต่ละค่า electron density ระหว่างภาพเอกซเรย์คอมพิวเตอร์ทั้งสองชนิดไม่แตกต่างกันอย่างมีนัยสำคัญ โปรแกรมวางแผนการรักษาและการลงทะเบียนภาพแสดงค่าที่ยอมรับได้ตามเกณฑ์ที่กำหนด และค่าความแตกต่างระหว่างการใช้ภาพเอกซเรย์คอมพิวเตอร์ลำรังสีรูปกรวยประจำวันและภาพเอกซเรย์คอมพิวเตอร์ที่ใช้ในการวางแผนการรักษาที่ปริมาตรของ CTV ที่ได้รับปริมาณรังสีที่ 100% เท่ากับ -0.1 ± 3.6% ซึ่งไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในขณะที่ค่าความแตกต่างของปริมาตรของ PTV ที่ได้รับปริมาณรังสีที่ 95% มีความแตกต่างที่ -6.7 ± 5.3% ความแตกต่างของปริมาตรของกระเพาะปัสสาวะโดยเฉลี่ยมีค่าเท่ากับ -23.6 ± 22.8% และค่าความแตกต่างของปริมาตรของลำไส้ตรงโดยเฉลี่ยมากกว่าแผนการรักษาเท่ากับ 16.8 ± 58.6% จากผลการศึกษาสรุปได้ว่าการเปลี่ยนแปลงของอวัยวะภายในนั้นไม่มีผลกระทบต่อ CTV และการขยายขอบเขต PTV เพียงพอต่อการควบคุมโรค แต่อย่างไรก็ตามกระเพาะปัสสาวะและลำไส้ตรงยังคงมีความแตกต่างและความแปรปรวนสูง โดยเฉพาะลำไส้ตรง ส่งผลทำให้เกิดอันตรายต่อเนื้อเยื่อปกติข้างเคียงเพิ่มมากขึ้น

สาขาวิชา	ฉายาเวชศาสตร์	ลายมือชื่อนิสิต .....
ปีการศึกษา	2561	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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KEYWORD: Daily CBCT, Hounsfield unit, Organs at risk, VMAT
Julaluck Chanayota :
Dosimetric comparison between using daily cone beam CT and planning CT in volumetri c modulated arc therapy technique for prostate cancer therapy. Advisor: Taweap Sanghangthum, Ph.D.

The variations of shape and size of organs inside, especially bladder and rectum, in prostate cancer patient are mainly factors of external beam radiation therapy that may impact to disease control and normal tissue toxicity. The purpose of this study was to investigate the dosimetric comparison between using daily CBCT and planning CT in Volumetric modulated arc therapy (VMAT) technique for prostate cancer therapy. The HU and electron density between CBCT and planning CT were verified by using Catphan® 600 phantom. Treatment planning system was verified by dose distribution comparison between plans on CBCT and planning CT images of Anthropomorphic RANDO® phantom. The dose on both images at central axis plan were transferred to Sun Nuclear Patient software to compare in terms of gamma index. Image registration software were also verified. The CBCT image were registered to CT image and the phantom was move to the known couch shifted. The CBCT was repeated and registered with CT. The registration errors were repeated. In clinical part, the total of seven cases with 299 daily CBCT images dataset were performed in this study. The patients were selected from selection criteria as follows with patients whom were diagnosed prostate cancer and already finished the course of VMAT prostate cancer treatment with 6 MV, 79.2 Gy prescription dose, 44 total factions. The structures of Clinical Target Volume (CTV), Planning Target Volume (PTV), bladder, and rectum on daily CBCT were contoured. The CTV was delineated in whole prostate including seminal vesicle and 8 mm margin in all directions except posterior that used 5 mm margin were expended to PTV following by RTOG 0815. The original plans were transferred into daily CBCT images and recalculated by Eclipse™ TPS. The volume difference of CTV $V_{100\%}$, PTV $V_{95\%}$, bladder and rectum at V_{75Gy}, V_{70Gy}, V_{65Gy} and V_{60Gy} were analyzed. For results, the HU and electron density was not significant between two imaging modalities. Treatment planning system and image registration showed good agreement on acceptable criteria. The volume differences of CTV at $V_{100\%}$ on average from all 7 patients were only -0.1 ± 3.6% that were not significantly different while the volume differences of PTV at $V_{95\%}$ was -6.7 ± 5.3%. The bladder volume difference were -23.6 ± 22.8% on average, while the average volumes difference of rectum was more than planning CT of 16.8 ± 58.6%. In conclusion, during course of prostate cancer treatment, organs inside always daily change. The changing is not impacts to dosimetric effect of CTV that means the CTV to PTV margin is enough expansion to disease control. However, the bladder and rectum show significant difference and large variations, especially rectum that have impact on normal tissue toxicity increased.

Field of Study: Medical Imaging Student's Signature .....
Academic Year: 2018 Advisor's Signature .....

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LIST OF ABBREVIATIONS

Abbreviations	**Terms**
3D-CRT	Three-dimensional conformal radiation therapy
AAA	Analytical anisotropic algorithm
CTP	Catphan phantom
cGy	Centi-Gray
cm	Centimeter
CTV	Clinical target volume
CT	Computed tomography
CBCT	Cone beam computed tomography
cm^3	Cubic centimeter
DIR	Deformable image registration
DTA	Distance to agreement
DVHs	Dose volume histograms
EBRT	External beam radiation therapy
ρ_e	Electron density
e.g	Exempli gratia, for example
EPID	Electronic portal image device
et al	Et alibi, and others
FOV	Field of view
Γ	Gamma index
Gy	Gray
HDR	High dose rate
HU	Hounsfield units
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiation therapy
kV-CBCT	Kilovoltage cone beam computed tomography
kVp	Kilovoltage peak
kVD	Kilovoltage digital imaging detector
kVS	Kilovoltage X-ray source

Linac	Linear accelerator
LDPE	Low density polyethylene
LDR	Low dose rate
MRI	Magnetic resonance imaging
MeV	Megaelectron-volts
MV	Megavolts
mA	Milliampere
mm	Millimeter
MU	Monitor units
MLC	Multileaf collimator
NPO	Nill per os
No.	Number
OBI	On-board imaging
OARs	Organs at risk
PTV	Planning target volume
PMP	Polymethylpentene
QA	Quality assurance
RIR	Rigid image registration
RTOG	Radiation therapy oncology group
SNC	Sun Nuclear Corporation
TLD	Thermaluminescence dosimeter
TPS	Treatment planning system
Vol.	Volume
VMAT	Volumetric modulated arc therapy

CHAPTER I
INTRODUCTION

1.1 Background and rationale

Currently, in worldwide considerably pay attention to prostate cancer as its most commonly diagnosed in males. It's rare among men under the age of 45 years, but more common after the age of 50 years. There are many treatment modalities such as surgery, chemotherapy, radiation therapy or multimodality treatment. The treatment modalities are depending on stages of cancer.

The external beam radiation therapy is the most common type of treatment modality used for clinically localized prostate cancer treatment depending on the characteristics of prostate cancer cells and stage of prostate cancer. The advantages of the external beam radiation therapy are non-invasive treatment and good responding, especially, the advance technique of external beam radiation therapy such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). The multileaf collimators (MLCs) are adjusted to conform the high radiation dose according to the shape of tumor and spare radiation dose to surrounding normal tissue. Conversely, the disadvantages of the external beam radiation therapy are the uncertainty of high radiation dose to target as the position of target changing during the course of treatment referring to the dosimetric error. There are three main steps to reduce the uncertainty in this technique. First, the CT simulation is performed to the patient. In this process, the images can show the locations of tumor and organs at risk and the setup area for patient positioning are presented on the skin of the patient. Moreover, CT images from CT simulation process are used for treatment planning process in the next step. Second, for the treatment planning process, the planning CT is used to define radiation dose for target and organs at risk. The organs at risk (OARs) located near or far the planning treatment volume (PTV) should be taken into consideration. Bladder and rectum are organs at risk of prostate cancer treatment. Normally, the protocol is prepared for controlling volumes of bladder and rectum to receive the dose lower than tolerance limits. The bladder and rectum volumes are varied during the course of treatment due to preparation protocol of the patients and

set up position. So, the bladder and rectum fillings are important factors for prostate cancer treatment. Several studies reported that the variation can impact to dosimetric difference that may influence to dose received in those organs or tumor controlling and affect to the probability of late radiation-related toxicities. The last step of external beam radiation therapy treatment is the verification process and treatment. Image guided radiation therapy (IGRT) has provided the powerful tools that mount the imaging device on the treatment machine for improving accuracy of patient positioning and target localization. The kV cone beam computed tomography (kV-CBCT) is one of IGRT types that can reconstruct in 3D high resolution image for treatment field verification purpose before treatment. Patient positioning can be verified by soft tissues and/or bony structures matching in CBCT to those in planning CT images. The kV-CBCT is not only show the image for verification, but also possible of presents the dose distributions via treatment planning. At present, the daily CBCT is widely used for the verification process in case of prostate cancer treatment and also can investigate actual dose receive at bladder and rectum.

Thus, the daily CBCT and planning CT can be used to determine the dosimetric differences between planning dose and actual dose that patient receive in target and organs at risk. The actual patient information was created by contouring and recalculating in daily CBCT image.

1.2 Objective

To investigate the dosimetric comparison between using daily cone beam CT and planning CT in volumetric modulated arc therapy technique for prostate cancer therapy.

CHAPTER II
REVIEW OF RELATED LITERATURES

2.1 Theory

2.1.1 Prostate gland

Prostate gland is a secretory organ of the male reproductive system. It's located below the urinary bladder, surrounds the urethra, and in front of the rectum. The seminal vesicles are attached to the prostate gland as shown in figure 2.1 [1].

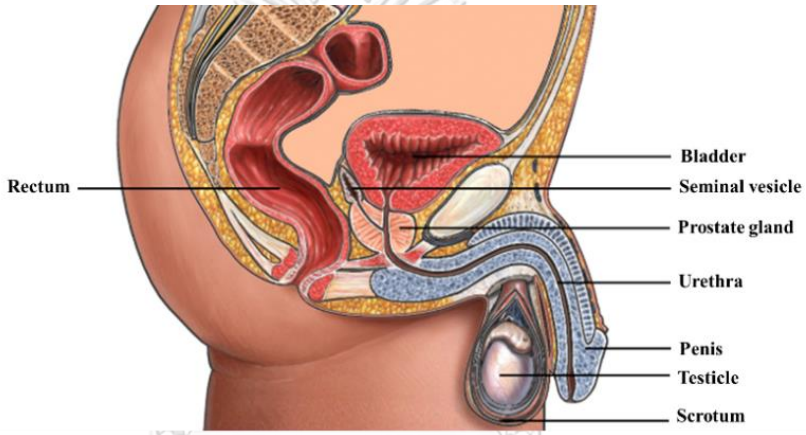


Figure 2.1 Diagram of the male reproductive system

2.1.2 Prostate cancer

The prostate cancer is the most commonly diagnosed cancer in men. In the United States, there are around 161,360 new diagnoses of prostate cancer, and around 26,730 deaths expected in 2017 [2]. The symptom of prostate cancer is obstructive urinary complains combined with axial or long bone pain, if the diseased metastasis. The diagnosis of prostate cancer is fairly simple when compare with most other malignancies. The prostate cancer can be diagnosed on digital rectum examination, transrectal ultrasonography, magnetic resonance imaging, computed tomography to determine the clinical staging. However, in each modality they are have inaccuracy of diagnosing and some conditions for patient. So, the biopsy specimen, histologic tumor grade (the Gleason grade) and pretreatment prostate specific antigen level are important adjunctive tools for prostate cancer patient.

2.1.3 Treatment options for prostate cancer

The best curative treatment for prostate cancer patient provides good disease control and good quality of life for patient's treatment options, it is usually helpful first to categorize the man according to clinical stage, the Gleason grade, patient age, comorbidity, and other factors (e.g., ploidy, personal beliefs) enter into the decision of which treatment is selected. The physician and patient can usually select the best treatment for each individual case such as radical prostatectomy, androgen ablation therapy, hormone therapy, chemotherapy, radiotherapy (External beam radiation therapy: EBRT and brachytherapy) or combined with multimodality [3].

EBRT and radioisotopic implantation (brachytherapy) are used to treat clinical localized prostate cancer, either alone or in combination. EBRT is a type of radiation therapy that uses a machine to aim high-energy rays at the cancer from outside of the body. EBRT alone may be applied to lesions of any clinical stage, T1 to T4, but is also often used with adjunctive antiandrogen therapy for selected patient. Brachytherapy is the insertion of radioactive sources directly into the prostate. These sources, called seeds, give off radiation just around the area where they are inserted and may be left for a short time high dose rate (HDR) or for a longer time low dose rate (LDR). Low dose rate seeds are left in the prostate permanently and work for up to 1 year after they are inserted. However, how long they work depends on the source of radiation. High dose rate brachytherapy, it involves inserting of applicators into the prostate gland. A source of radiation is then passed down the applicators into the prostate for a few minutes to destroy cancer cells, but it may require to be given more than once.

In terms of similarity both teletherapy and brachytherapy techniques are good responding. EBRT is non-invasive treatment, while brachytherapy is invasive treatment and complex of methods. Thus, the EBRT is widely used for clinical localized prostate cancer.

2.1.4 External beam radiation therapy

The 4 steps of radiation therapy for VMAT prostate cancer are described in the following details.

2.1.4.1 Treatment simulation

Before treatment simulation, firstly, the prostate cancer patient is recommended to take a laxative drug to empty the feces and air for 1-2 days. Secondly, all patients are required to nill per os (NPO) at least 6 hours prior simulation since they have to receive contrast media for lymph node evaluation. Finally, all patients will be waiting until the bladder is full.

At the time of treatment simulation, the patients are lied down on the CT couch with the supine position. Then, the patients are undergoing CT scan with pelvis exposure protocol for assessed the internal organ in the prostate portion. Radiation oncologist and radiation therapist observe the gas or feces in rectum. The rectum will be cleared again at that time whether they found unnecessary issues. After that, the CT scanned for planning in the region of interest of the patients were undertaken. The CT information is useful in two aspects of treatment planning, it can delineate the target volume and the surrounding structures in relation to the external contour and can provide quantitative data (in the form of CT numbers) for tissue heterogeneity corrections.

2.1.4.2 Treatment planning

Treatment planning is the method include contouring, arrangement of the suitable beam direction, plan optimization, dose calculation based on the 3D images such as CT and MR images and plan evaluation. Usually, the CT is the gold standard images for radiotherapy planning since they provided the accurate patient contouring, and difference value of Hounsfield unit (HU) related to electron density for radiation dose calculation as shown in figure 2.2 [4]. Furthermore, the variety of HU is useful for inhomogeneity correction for the accurate dose calculation in EBRT.

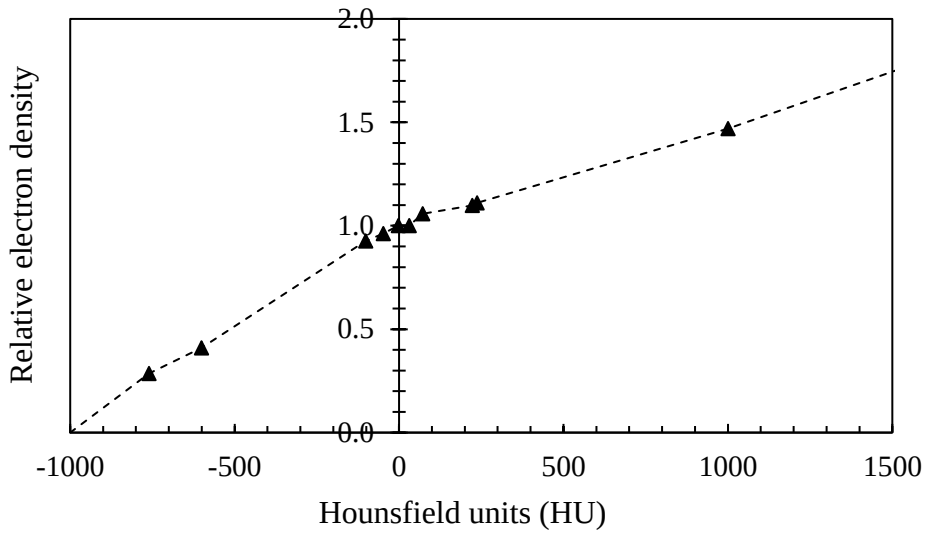


Figure 2.2 The HU and electron density calibration curve

For prostate cancer treatment, the high concentrated dose more than 79.2 Gy is aimed to deliver to the prostate gland plus the margins as planning target volume (PTV) for killing the cancerous cell while reducing the dose to neighboring normal tissues as low as possible. Dose limitation for all organs at risk (OARs) for prostate cancer patient treatment followed Radiation therapy oncology group (RTOG) guideline number 0815 is illustrated in table 2.1 [5].

Table 2.1 Dose limitation of adjacent OARs for prostate cancer radiotherapy according to RTOG report number 0815

Normal organ limits	No more than 15% volume receives dose that exceeds	No more than 25% volume receives dose that exceeds	No more than 35% volume receives dose that exceeds	No more than 50% volume receives dose that exceeds
Bladder Constraint	80 Gy	75 Gy	70 Gy	65 Gy
Rectum Constraint	75 Gy	70 Gy	65 Gy	60 Gy
Penile Bulb	Mean dose less than or equal to 52.5 Gy			

The types of treatment planning technique are as following

Three dimensional-conformal radiation therapy (3D-CRT): A radiation treatment that shapes of the radiation beams using fixed position of multileaf collimator (MLC) in each field to match the shape of the tumor. Conformal radiation therapy uses the targeting information to focus precisely on the tumor, while avoiding the healthy surrounding tissues. This exact targeting makes it possible to use higher levels of radiation in treatment. More radiation is more effective in shrinking and killing tumors.

Intensity modulated radiation therapy (IMRT): In short, a type of advanced conformal radiotherapy. Conformal radiotherapy shapes the radiation beams to closely fit the area of the cancer. IMRT can form shapes that fit precisely around the treatment area. The MLC can move to modulate the beam intensity in each gantry angle. The IMRT plan is found to significantly reduce the normal tissue complication for the rectum while achieving a small gain in tumor control [6].

Volumetric modulated arc therapy (VMAT): An advanced form of modulated radiotherapy technique to reach the goal of radiotherapy. In this technique, the machine continuously reshapes and changes the intensity of the radiation beam as it moves around the body. VMAT can achieve highly conformal dose distributions with improved target volume coverage and sparing of normal tissues compared with conventional radiotherapy techniques by using dynamic MLC movements, varying dose rate, gantry and MLC speed. Moreover, this technique also has the potential to offer additional advantages as dramatically decreased the treatment time compared with fixed beam IMRT. All approaches yield treatment plans of improved quality when compared to 3D-conformal treatments, with IMRT providing best OAR sparing and VMAT being the most efficient treatment option in our comparison. Plans which are calculated with 3D-CRT provided good target coverage but resulted in higher dose to the rectum for the prostate cancer [7].

2.1.4.3 Dosimetric verification

To ensure the Linac machine delivered the radiation dose to patient correctly, the patient specific QA should be verified prior to the first treatment by medical physicist.

The gamma index was commonly used for 2D or 3D dosimetric verification between TPS dose calculation and measured dose.

The gamma method, as prepared by Low et al. [8], was designed for the comparison of two dose distributions: one is defined to be the reference information ($D_r(r)$) and the other is queried for evaluation ($D_c(r)$). Figure 2.3 shows a schematic representation of the gamma analysis tool for two-dimensional dose distribution evaluations. The acceptance criteria are denoted by ΔD_M for the dose difference and Δd_M for the distance to agreement DTA). For a reference point at position r_r, receiving dose D_r, the surface representing these acceptance criteria is an ellipsoid defined by:

$$1 = \sqrt{\frac{\Delta d^2}{\Delta d_M^2} + \frac{\Delta D^2}{\Delta D_M^2}}$$

where $\Delta r = |r_r - r_c|$ is the distance difference between the reference and compared point and $\Delta D = D_c(r_c) - D_r(r_r)$ is the dose difference at the position r_c relative to the reference dose D_r in r_r. For the compared distribution to match the reference dose in r_r, it needs to contain at least one point (r_c, D_c) lying within the ellipsoid of acceptance, i.e. one point for which:

$$\Gamma_r(r_c, D_c) \equiv \sqrt{\frac{\Delta d^2}{\Delta d_M^2} + \frac{\Delta D^2}{\Delta D_M^2}} \leq 1$$

A quantitative measure of the accuracy of the correspondence is determined by the point with the smallest deviation from the reference point, i.e. the point for which $\Gamma_r(\boldsymbol{r_c}, Dc)$ is minimal. This minimal value is referred to as the quality index $\gamma(r_r)$ of the reference point.

The pass–fail criterion therefore becomes:

$\gamma(r_r) \leq 1$, correspondence is within the specified acceptance criteria,

$\gamma(r_r) > 1$, correspondence is not within specified acceptance criteria.

An implicit assumption is made that once the passing criteria are selected, the dose difference and DTA analyses have equivalent significance when determining calculation quality.

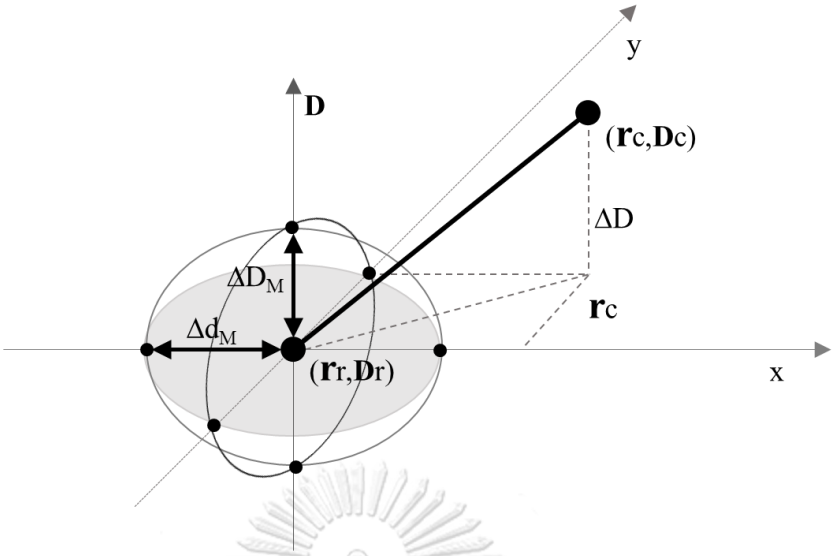


Figure 2.3 Schematic representation of the theoretical concept of the gamma evaluation method

2.1.4.4 Treatment field verification and dose delivery

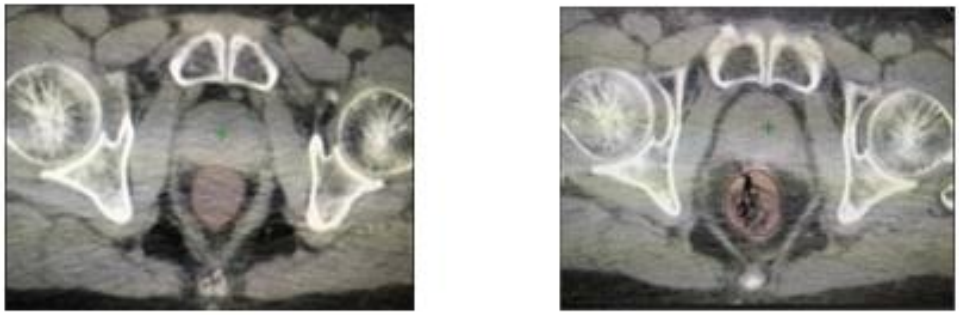
Before radiation dose delivery, image-guided radiation therapy (IGRT) is required to verify patient position. Currently, the routine IGRT such as kV and MV planar imaging and kV-CBCT are contributed to improve the accuracy of treatment, and they provide the good treatment outcome as depicted in several study [9, 10].

MV planar image is developed from the plan film, but it is acquired by electronic portal imaging device (EPID) and used to verify the patient position with the direction of treatment field as called “portal imaging”. The advantages of this technique are the fast technique and appreciated for breast cancer patient localization. However, the drawback is the poor image contrast.

Orthogonal kV planar imaging is one of planar radiographic that provides the better contrast when comparing with MV planar image. It presents the benefit for the tumor location related to the bony landmark such as spine, skull and extremity. However, this technique just provides only 2D information, consequently it does not present the internal anatomical of tumor target and adjacent normal tissues.

Kilovoltage cone beam computed tomography (kV-CBCT) is the most commonly IGRT that used to patient position verification. It is the beneficial tool to assess patient position before treatment since it provided the 3D information and internal

organ variations. However, radiation technician staff are able to observe the patient anatomy during the course of treatment and consequently can decide for adaptive radiotherapy planning. This IGRT shows the vital roles to manage and noticed the internal structures particularly in head and neck, lung, abdomen and prostate cancer patient [11]. The example of rectal volume deviation between planning CT and daily CBCT in prostate cancer patient. This effect may impact on the accuracy of radiation dose to target volume and all nearby OARs as shown in figure 2.4.

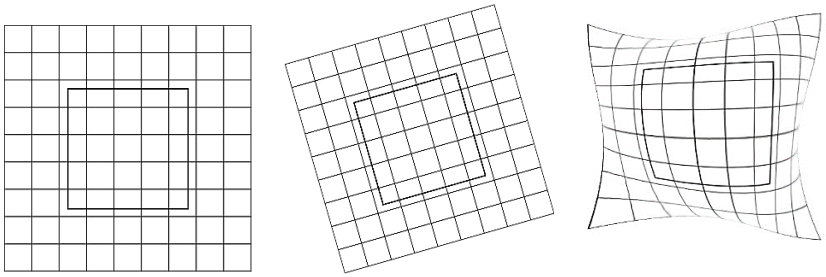


(A) (B)

Figure 2.4 The changing of rectal volume during the radiotherapy course comparison between (A) planning CT and (B) CBCT before treatment

The image registration is performed during treatment field verification process. It is the geometric transformation that related the coordinate system of two image data set. Image registration can be categorized into two groups: rigid image registration (RIR) and non-rigid image registration, non-rigid image registration is also known as deformable image registration (DIR). In rigid image registration, all pixels move and/or rotate uniformly so that every pixel-to-pixel relationship remains the same before and after transformation. In DIR, however, those pixel-to-pixel relationships change as presented in figure 2.5. The RIR is used in radiation therapy (e.g., CT-to-MR registration, CT-to-CBCT registration). It is widely recognized that RIR is very effective in cases when no anatomic change is expected. Sometimes, however, patients do experience anatomical structure changes due to weight loss, tumor shrinkage, and/or physiological organ shape variation, which often cannot be handled by RIR at all. In comparison to RIR, the DIR is a significantly greater number of

degrees of freedom (DOF). Therefore, DIR can manage local distortion between two image sets (i.e., anatomical structure changes) [12, 13].



(a) (b) (c)

Figure 2.5 The example of different types of transformations of a square (a) identity transformation, (b) rigid transformation, and (c) non-rigid transformation

2.2 Review of related literature

Yoo S, et al [14] studied in HU & electron density verification and dosimetric feasibility of cone beam CT based on treatment planning and compared to the dose on CT based treatment planning. The purpose of this study was to investigate the dosimetric feasibility of CBCT-based treatment planning. CT scan and CBCT scan were performed to the Catphan phantom, Homogeneous/Inhomogeneous phantoms and various tissue regions of patients with in/out bowtie filter for all phantom and with bowtie filter for patients and then the image artifact, HU comparison and dose comparison were evaluated.

The results found that HU differences between CBCT image and CT image of Catphan were less than 10 HU except Teflon, MU/cGy differences were lesser than 1% for most phantom cases, the isodose distributions agreed very well except CBCT without bowtie filter and the discrepancies of isodose lines for the patient studies between CT based and CBCT-based plans were less than 2 mm. The authors suggested that CBCT based treatment plans were dosimetrically comparable to CT-based treatment plans, since the dosimetric results in CBCT-based plans were comparable to the results in CT-based plans. In spite of CBCT images certainly include larger scatter and artifacts than CT images and difference of HU value. However, if CBCT is used for the treatment planning purpose, CBCT should be scanned using a bowtie filter. Dosimetric data in the inhomogeneous tissue regions should be carefully validated.

Pearson D, et al [15] studied the dosimetric and volumetric changes in the rectum and bladder in patients receiving CBCT-guided prostate IMRT: analysis based on daily CBCT dose calculation. This study purposed to analyze and quantify the actual dose received by the bladder and rectum during an entire course of radiotherapy with respect to daily changes in the shape and volume of these organs. The 6 prostate cancer patients were used in this study. All patients were treated by external beam radiation therapy with IMRT technique and daily CBCT were performed for treatment field verification as the routine's treatment processes. They daily CBCT images were retrospective to re-contour (CTV, bladder and rectum) and re-calculate based on

original plan on planning CT. Finally, dose and volume between planning CT and daily CBCT were compared.

The results showed that the cumulative doses in CTV for 6 patients by average over all CBCTs at $V_{95\%}$ was 99.95% and the volume of bladder and rectum have changed. The cumulative of bladder at V_{70Gy} changed from 9.47% on the planning CT to 10.99% on the average of all daily CBCT and the cumulative of rectum at V_{70Gy} changed from 7.27% on the planning CT to 11.56% on the average of all daily CBCTs. In conclusion, volumetric dose received by the rectum and bladder significantly differ as compared to planned dose due to the changes in shape and size of these organs as shown in figure 2.6. The authors suggested that the bladder and rectum volume should be kept consistent, or as close as possible, on a daily basis, for patients undergoing treatment.

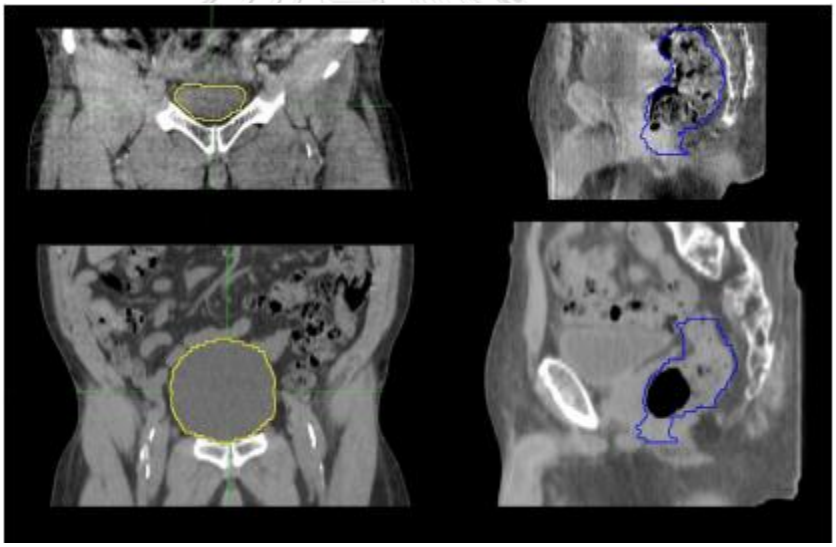


Figure 2.6 The change in bladder (left) and rectum (right) volume on planning CT (bottom) and daily CBCT

Chen Z, et al [16] studied dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy. They purposed to track the volume and dosimetric changes in the bladder and rectum based on daily cone-beam CT in 19 prostate cancer patients. The patients were required to drink a glass of water about 30 mins before the acquisition of treatment planning CT under the supervision of physicians. Also, the patients were reminded to drink the same amount of water 30

mins before each fractional treatment. The 314 cone-beam CT (CBCT) image datasets of every patients were contoured in bladder and rectum and volume sizes were normalized to those on their original CT. The daily delivered dose was recalculated on the CBCT images and the doses to bladder and rectum were investigated. The mean volume change was performed by linear regression analysis. The results showed that bladder's volume change is more significant than that of the rectum for the prostate cancer patient. The rectum volume variations are not significant except for air bubbles, which change the shape and the position of the rectum. The bladder volume variations may cause dose changes proportionately. Monitoring the bladder's volume before fractional treatment delivery will be crucial for accurate dose delivery.

CHAPTER III
RESEARCH METHODOLOGY

3.1 Research design

This research was observational descriptive study with retrospective from prostate cancer patients who completed the course of treatment before June 2018.

3.2 Research design model

This research was divided into 4 major steps. The first step was verification of HU and electron density of CBCT images. Then, determination of treatment planning system verification in Eclipse™ was performed. The next step was image registration software verification with CBCT guided, and the last step was the daily dosimetric determination according to daily CBCT images. Figure 3.1, 3.2, 3.3, and 3.4 display the diagram of the each step in this research according to the above explanation.

3.2.1 HU and electron density verification

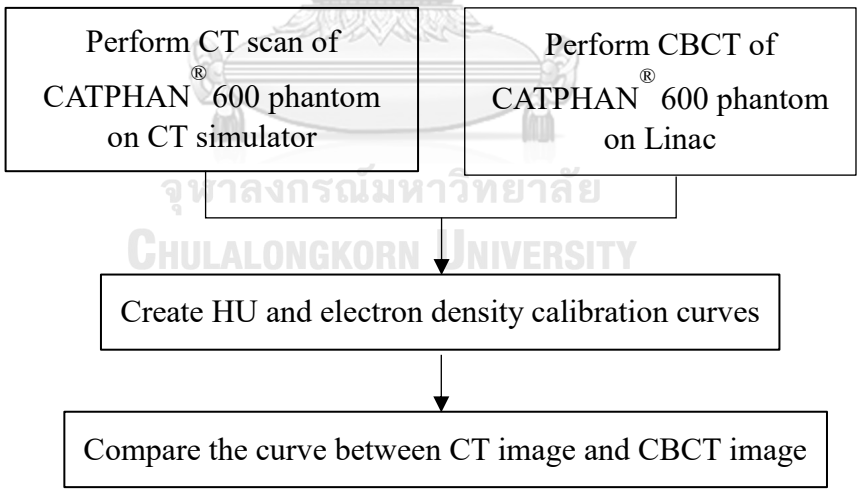


Figure 3.1 Research design model of HU and electron density verification

3.2.2 Treatment planning system verification

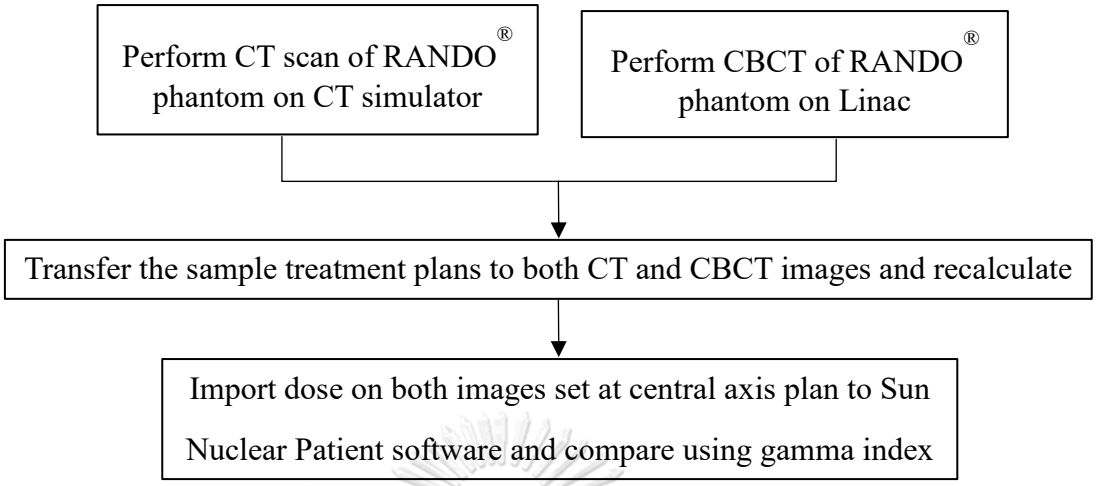


Figure 3.2 Research design model of treatment planning system verification

3.2.3 Image registration software verification

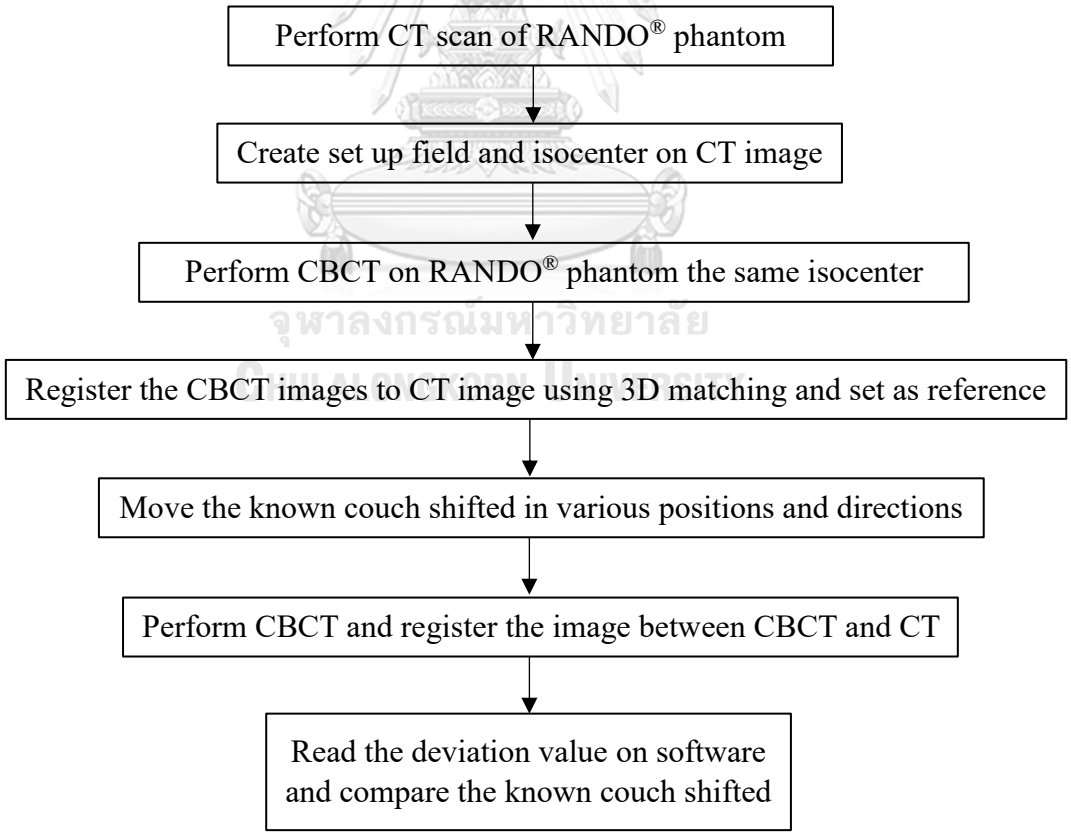


Figure 3.3 Research design model of image registration software verification

3.2.4 Daily dosimetric determination in clinical part

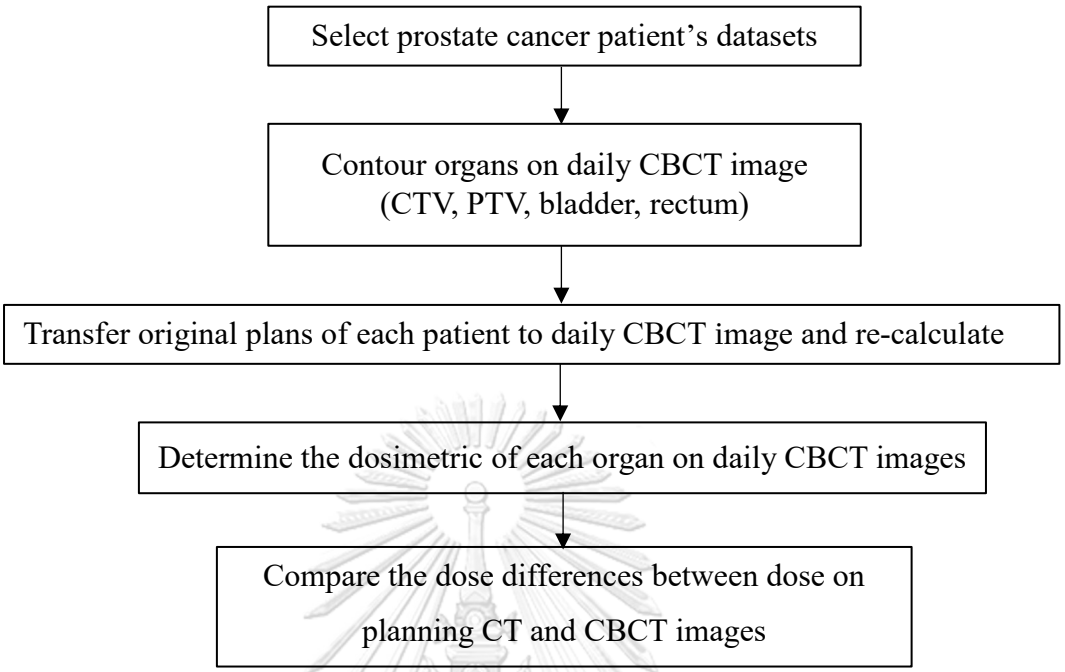


Figure 3.4 Research design model of daily dosimetric determination in clinical part

3.3 Conceptual framework

Validation of VMAT prostate plan by dose difference between using planning CT and daily CBCT in this study was affected by several factors as shown in figure 3.5.

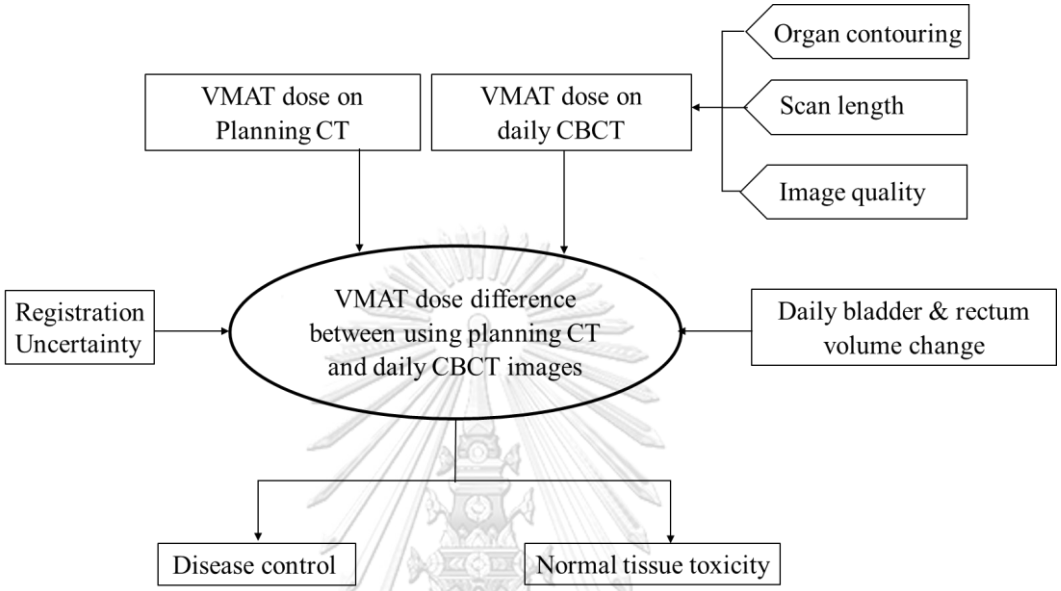


Figure 3.5 Conceptual framework

3.4 Research question

What are the dosimetric differences between using daily cone beam CT and planning CT in volumetric modulated arc therapy technique for prostate cancer therapy?

3.5 Materials

The materials used in this study were supplied from the Division of Radiation Oncology, King Chulalongkorn Memorial Hospital.

3.5.1 Linear accelerator

The linear accelerator or Linac is the external beam radiation treatments machine. Linear accelerator is used to treat the cancer patient. It can deliver high-energy x-rays or electrons to the region of the patient's tumor. This research employed Varian TrueBeam™ linear accelerator (Varian Medical System, Palo Alto, CA, USA) as shown in figure 3.6. The linear accelerator provides all forms of advanced external beam radiotherapy including 3D-CRT, IMRT, and VMAT techniques. This Varian TrueBeam™ linear accelerator provides two photon energies: 6 MV and 10 MV in both flattened and unflattened photon beams. The electron beams are also provided in various energies: 6, 9, 12, 15, 18, and 22 MeV with 120-leaf multileaf collimators (MLCs). For this study, the 6 MV with flattenning filter (flattened) photon beams was used with VMAT plan to treat prostate cancer patient.

The on-board imaging (OBI®, Varian Medical System, Palo Alto, CA, USA) is mounted on gantry as the robotic arm on Varian TrueBeam™ Linear accelerator system and consists of a kV X-ray source (KVS) and a kV amorphous-silicon digital imaging detector (KVD) as shown in figure 3.6. The CBCT images were reconstructed using about 700 kV-projection images acquired over 360° rotation and reconstructed post processing image by filter back projection. When the center of the KVD is positioned at the isocenter in the longitudinal-lateral plan and 50 cm away from the isocenter in the vertical direction, the reconstructed field-of-view (FOV) is a circle of 24 cm diameter with a 15 cm length. This acquisition mode is called “full-fan” and is used for small anatomic sites such as the brain, head-and-neck, and a truncated part of larger sites. For larger sites, such as the pelvis, chest, and abdomen only part of the object is viewed in a half-fan projection and the other part of the object is viewed in the half-fan projection from the opposite direction. This acquisition mode is called “half-fan”. The FOV for the half-fan mode is a circle of 45 cm diameter with a 14 cm length. The effects of X-ray scatter and artifacts are larger

in CBCT images than in CT images. A bowtie filter is mounted to the X-ray tube to improve image quality by reducing intensity variations across the detector. In this work, the daily kV-CBCT was used to verify the patient positioning before prostate cancer patient treatment.

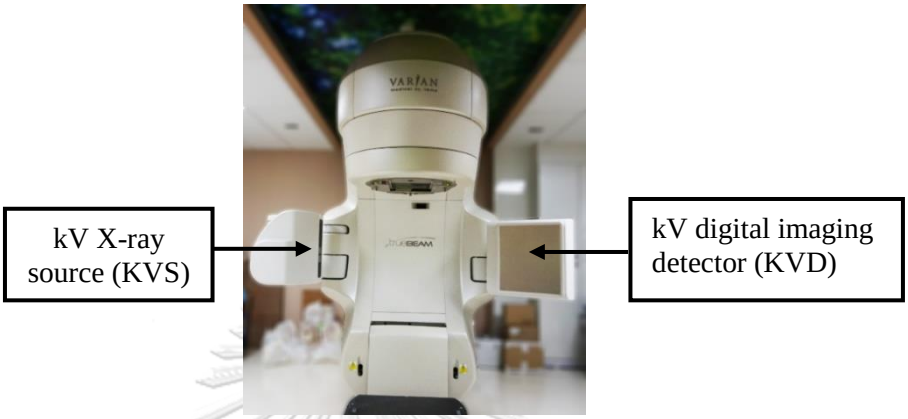
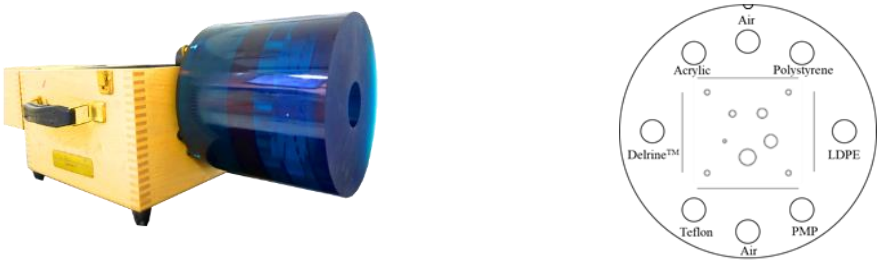


Figure 3.6 The linear accelerator with kV-CBCT

3.5.2 Catphan® 600 phantom

The Catphan® 600 phantom (The Phantom Laboratory, Inc., Greenwich, NY, USA) as shown in figure 3.7, (A) was used to verify the HU and electron density from CT simulator and kV-CBCT. The Catphan® 600 phantom is set in air at the end of the box placing on couch. The phantom is adjusted by precisely indexing the couch from the center of section 1 (CTP404 section). The CTP404 module is the first section of the Catphan® 600 phantom. The details of CTP404 module consists of eight sensitometry samples (Teflon, Delrin™, Acrylic, Polystyrene, Low density polyethylene (LDPE), Polymethylpentene (PMP) and two of air as shown in figure 3.7 (B). These targets range from approximately +1000 HU to -1000 HU.



(A) **(B)**

Figure 3.7 (A) Catphan® 600 phantom and (B) cross sectional of CTP404 section

Relative electron densities were used to plot with HU values. The relative of electron density can be determined by the electron density of any material in e/cm^3 divided by the electron density of water (H_2O) in e/cm^3 as displayed in table 3.1.

Table 3.1 Electron density and relative electron density

Materials	Specific activity (g/cm^3)	Electron density ($10^{23}e/g$)	Electron density ($10^{23}e/cm^3$)	Relative electron density
Air (upper)	0.001	3.007	0.003	0.001
Air (lower)	0.001	3.007	0.003	0.853
PMP	0.830	3.435	2.851	0.945
LDPE	0.920	3.429	3.155	0.998
Polystyrene	1.050	3.238	3.399	1.000
Acrylic	1.180	3.248	3.833	1.147
Delrin®	1.410	3.209	4.524	1.368
Teflon®	2.160	2.889	6.240	1.868

3.5.3 CT simulator

A Brilliance 16 slice Philips Healthcare CT simulator (Phillips Healthcare, Inc., Cambridge, MA, USA) as shown in figure 3.8 is used to perform CT images. The characteristics of CT simulator are 85 cm bore size to accommodate patients in immobilization devices or with bulky patient monitoring devices. The flat couch is designed to be the same as the couch of Linac. External laser system was another characteristic of CT simulator that consisted of 4 positioning lasers on left side, right side, inferior side and ceiling same as the laser system in linear accelerator machine. For pelvis scan, 120 kVp and an automatically adjusted mA with 3 mm slice thickness were set. Although the automatically adjusted mA technique is used, mA during scanning is consistently found to be 80 to 110 mA for pelvis scan.

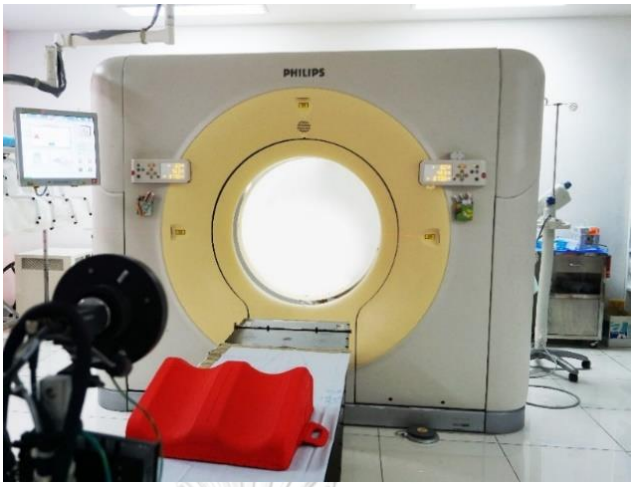


Figure 3.8 Philips Healthcare CT Brilliance16 slice simulator

3.5.4 Anthropomorphic RANDO® phantom

Anthropomorphic RANDO® phantom (The Phantom laboratory, Salem, NY, USA) as exhibited in figure 3.9, is molded of tissue-equivalent material. RANDO® phantom incorporates the materials to simulate various tissues such as muscle, bone, lung, and air cavity. RANDO® phantom provides the detailed mapping of dose distribution that is essential for evaluating radiotherapy treatment plans. There are two RANDO® models: RANDO® Man and RANDO® Woman. RANDO® phantoms are constructed with a natural human skeleton cast inside material that is radiologically equivalent to soft tissue. RANDO® phantom is transected-horizontally into 2.5 cm thick slices. Each slice has holes which are plugged with bone equivalent, soft tissue equivalent or lung tissue equivalent pins and can be replaced by TLD holder pins for in vivo dosimetry [17, 18].

Figure 3.9 Anthropomorphic RANDO® phantom

3.5.5 Eclipse™ treatment planning system

Eclipse™ treatment planning system software Version 11.0.31, (Varian Medical Systems, Inc., Palo Alto, CA, USA) as shown in figure 3.10 is an integrated and comprehensive treatment planning system to support the external beam radiation therapy such as photon (3D-CRT, IMRT, VMAT technique), electrons, protons, low-dose-rate brachytherapy, and cobalt therapy. There are two photon dose calculation algorithms: Analytical Anisotropic Algorithm (AAA) and Acuros XB algorithm. The AAA algorithm was used to calculate the prostate dose distribution in this study, Eclipse™ TPS allows clinicians to efficiently create the organs and calculate the best treatment plans for their patients [19].

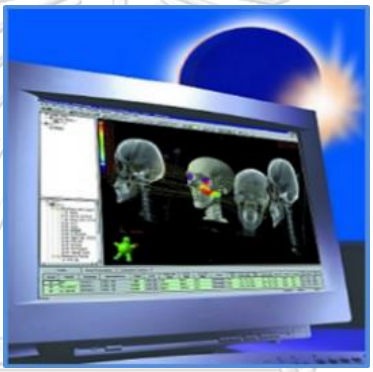


Figure 3.10 Eclipse™ treatment planning software

3.5.6 Sun Nuclear Patient software

The advance treatment technique such as IMRT and VMAT requires to the patient specific QA to verify the accuracy of MLC movement in each patient. Modern patient plans are often collections of small beamlets with very steep dose gradients. Since these dose gradients are tightly conform to patient anatomy and PTV, an accurate verification of the dose gradient is critical. SNC patient software (SUN Nuclear Corporation, Melbourne, FL, USA) is able to compare the plane or volume dose difference and presents in terms of gamma passing rate. This research employed SNC patient software to evaluate 2D planar dose difference at central axis [18].

3.6 Methods

The methods were divided into two sections. The first section was to verify factors that impact to results of research. The second part was the section of daily dosimetric determination in clinical part.

3.6.1 Verification of image system

3.6.1.1 HU and electron density verification

The CT scanner and kV-CBCT were employed to verify the correlation between HU and electron density curves. The relationship of HU and electron density was used for inhomogeneity correction during dose calculation. The HU and electron density verification steps must be performed for the following Catphan® 600 phantom manual.

The procedures of measurement of HU values from CT and CBCT image were as followings:

1. The wooden Catphan phantom storage box was set on the couch of CT scanner, and the Catphan phantom was attached in the storage box. The lateral phantom was set by longitudinal laser and the vertical direction of phantom was set by vertical lasers. Figure 3.11 is an example of how the setup looks like.

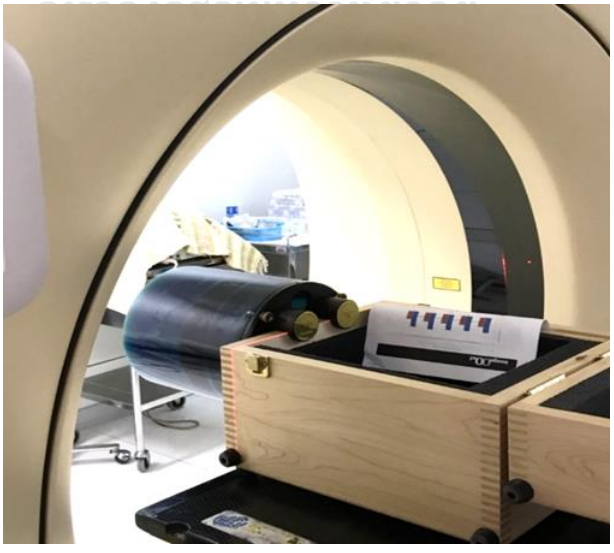


Figure 3.11 Catphan® 600 phantom setup for CT simulator

The scanning parameters of CT were pelvis protocol, single-energy with 120 kVp, helical mode scan, 325 mAs. The 250 mm FOV, 3 mm slice thickness, 521x512 matrix size, and 1.0 pitch were set. All of the sections of phantom were scanned and reconstructed.

2. The Catphan® 600 phantom was positioned on the couch of linear accelerator using the wall lasers or filed light for alignment. The lateral phantom was set by longitudinal laser and the vertical direction of phantom was set by vertical lasers as displays in figure 3.12.

Figure 3.12 Catphan® 600 phantom setup for linear accelerator

The scanning parameters of CBCT were standard pelvis mode, half bow-tie, full scan mode, 1,080 mAs, and 512x 512 matrix size after reconstruction.

3. The HU of each element in the CTP404 section module was measured at the center of elements.

4. The HU values of each element from CT and CBCT image were used to verify accuracy of calculation of treatment planning. The HU values of all materials from CT image (CTP404 section) were sorted from high to low. The curve was plotted between HU values and electron density for each material and the processes were repeated for CBCT image. The two curves from CT image and CBCT image of the Catphan® 600 phantom (CTP404 section) were compared.

3.6.1.2 Treatment planning system verification

Treatment planning was used to simulate the parameters of radiation machine for patients before treatment. The parameters for accurate target localization and good beam design in order to produce high dose to tumor and low dose to normal tissues, such as the suitable beam orientations and field size, and number of beams were selected. In this procedure, the same condition of planning parameters to determine the dose difference between these two images modality (CT image and CBCT image) were performed.

The procedures of comparison of the dose difference between using CT planning and CBCT planning were as followings:

1. Anthropomorphic RANDO® phantom was positioned on the couch of CT simulator and Linac machine using laser system to setup the phantom at isocenter position. The lateral phantom was set by longitudinal laser and the vertical direction of phantom was set by vertical lasers with isocenter at pelvis.

2. The phantom was scanned by two imaging modalities of CT simulator and kV-CBCT using pelvis mode.

3. The VMAT original plans from patient's treatment plans were transferred to these two imaging modalities (CT simulator and CBCT) and recalculated in treatment planning system.

4. The central axis dose plane of two imaging modalities was exported from Eclipse TPS and imported to Sun Nuclear Patient software. The 2D dose plane from planning CT and CBCT were compared in terms of gamma index (3%/3mm, 2%/2mm, and 1%/1 mm of the gamma passing rate) as shown in figure 3.13.

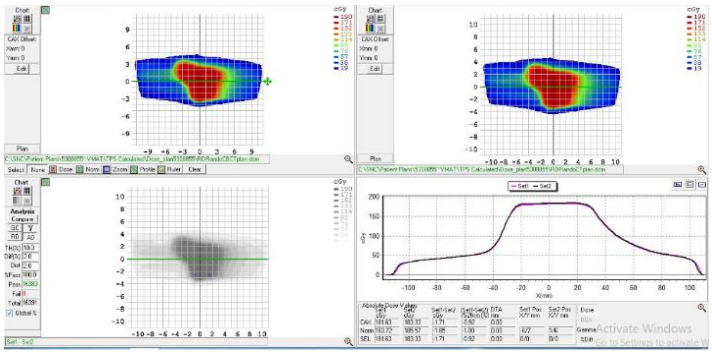


Figure 3.13 2D Plane dose comparison between CT and CBCT on SNC patient software

3.6.1.3 Image registration software verification

Image registration software was used to register the two imaging modalities (geometric alignment of one image with another). The image registration process was used in wide paradigms such as treatment planning system and treatment delivery.

The procedures of verification of image registration software were as followings:

1. The images of Anthropomorphic RANDO® phantom that scanned in previous CT simulation process were used in this procedure.

2. The CBCT images of Anthropomorphic RANDO® phantom was performed.

3. The 3D matching was undertaken by matching bony structures of CBCT to planning CT image and set to reference value.

4. The treatment couch was shifted to the known values of +1 mm and -1 mm in lateral direction and the CBCT was performed.

5. The CBCT image was registered with planning CT and the distance difference were record.

6. The fourth and fifth steps were repeated in longitudinal and vertical directions.

7. The fourth to sixth steps were repeated with the values of 3, 5, 10, 15, and 20 mm shifted.

3.6.2 Daily dosimetric determination in clinical part

The patient data of this procedure were retrospective study. A total of seven cases with 7 planning CT and 299 CBCT image data set were studied. The patients were selected based on the selection criteria as following: patients whom were diagnosed with prostate cancer without lymph-node involvement and completed treatment of the course of VMAT prostate cancer treatment with daily CBCT. Each patient data set consisted of 1 planning CT image set with organ contoured by the radiation oncologist and dose distribution from VMAT plan and 44 daily CBCT image set.

The procedures of comparison of the dose difference between CT planning and CBCT planning were as followings:

1. All daily CBCT images that registered with planning CT by 3D matching bony structures and following by soft tissues matching on PTV were evaluated. The window level was adjusted on abdomen window. The structures of CTV, PTV, bladder, rectum and body were contoured in actual positions by researcher and approved by radiation oncologist. The CTV was delineated in whole prostate including seminal vesicle and 8 mm margin in all directions except posterior that used 5 mm margin were expended to PTV. The 6 MV VMAT technique was planned by Eclipse treatment planning system with 79.2 Gy prescribed dose in 44 fractions and defined as the original plan.

2. The original plans were transferred into CBCT images and recalculated by fixing Monitor units (MU) that was represented to the real dose patient received according to the actual organ positions

3. The dose distribution were presented on CBCT planning. The Dose Volume Histograms (DVHs) was represented in absolute dose and absolute volume correlation. The DVHs were used to analyze the dosimetric and volumetric of dose difference of CTV at $V_{100\%}$, PTV at $V_{95\%}$, bladder and rectum at V_{75Gy}, V_{70Gy}, V_{65Gy}, and V_{60Gy}.

4. Data analysis were performed by the percentage of volume difference at any dose received by these organs and compared using planning CT and daily CBCT planning. The percentage of volume difference of CTV at $V_{100\%}$, PTV at $V_{95\%}$, bladder and rectum at V_{75Gy}, V_{70Gy}, V_{65Gy} and V_{60Gy} were analyzed by equation,

$$\text{Volume difference (\%)} = \frac{\text{CBCT vol.} - \text{Planning CT vol.}}{\text{Planning CT vol.}} \times 100$$

3.7 Statistical analysis

The paired T-Test was used to compare the dose and volume differences between using planning CT and daily CBCT images.

3.8 Sample size determination

The sample size determined using equation by following,

$$N = \frac{(z_{\alpha/2})^2(\sigma)^2}{[d]^2}$$

Where: N = Sample size

$Z_{\alpha/2}$ = 95% confident level (1.96) $\alpha = 0.05$

σ = Variance of data (4) (from literature review)

d = Acceptable error (3)

$$N = \frac{(1.96)^2(4)^2}{[3]^2} = 6.96$$

3.9 Outcome measurement

Actual patient doses from calculation based on actual organ positioning on daily CBCT and the percentage of volume difference and variations of all interesting organs.

3.10 Benefits of research

This research was helpful to obtain the actual patient dose information. In addition, the variation of the organs at risk from contouring in daily CBCT image was gainful to predict radiation dose of bladder and rectum for patients in the future.

3.11 Ethical consideration

This research involves the dosimetric comparison between using daily CBCT and planning CT in VMAT technique for prostate cancer therapy. The dosimetric are collected from treatment planning system. The research proposal submitted and approved by Ethic Committee of Faculty of Medicine, Chulalongkorn University, and Bangkok, Thailand (IRB NO. 301/61). The certificate is shown in APPENDIX B.

CHAPTER IV
RESULTS

The results were separated into 2 parts: the verification and clinical application of image system.

4.1 Verification of image system

4.1.1 Hounsfield unit and electron density verification

The result of HU and relative electron density of various materials in CTP404 section of the Catphan® 600 phantom from CBCT image compared with CT simulation image as the reference is shown in figure 4.1. The HU and relative electron density relationship of these two imaging modalities was very good agreement. The HU differences were less than 50 HU for all materials except Teflon, the highest density material, which presented the difference of 108 HU value or 12%.

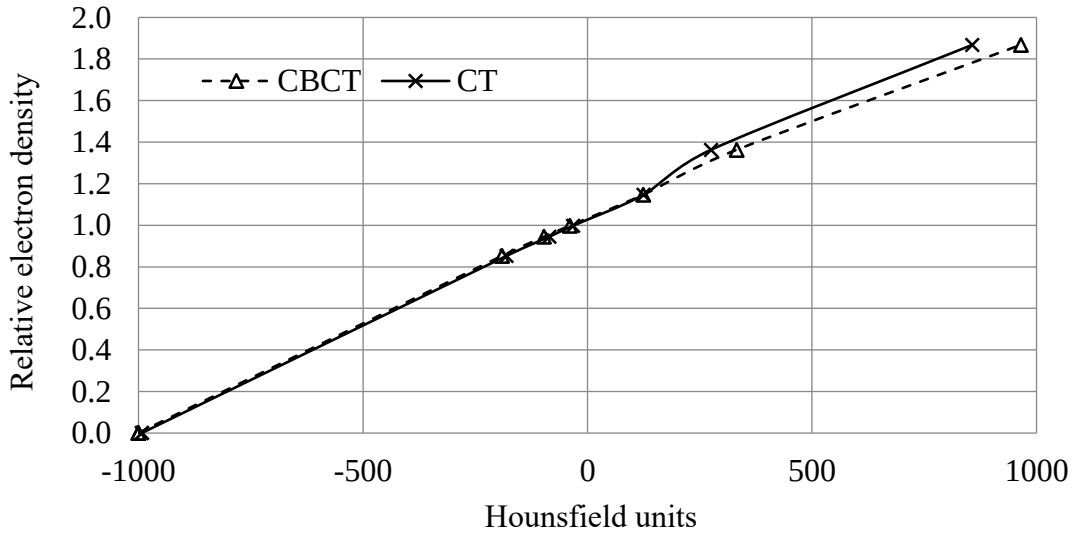


Figure 4.1 Hounsfield units and relative electron density comparison in CT image and CBCT image

4.1.2 Treatment planning system verification

The original HU and relative electron density from CT simulation was applied and dose distribution of each plan was calculated. The example of VMAT original plans from patient's treatment plans were recalculated with CT and CBCT image of Anthropomorphic RANDO® phantom. The 2D dose plane from planning CT and

CBCT were compared in terms of gamma index by Sun Nuclear Patient software to confirm the accuracy of dose distribution. The gamma results at 2D central axis dose plane differences between using CBCT and planning CT were 100%, 100%, 95.2% for 3%/3mm, 2%/2mm, and 1%/1 mm gamma criterion, respectively.

4.1.3 Image registration software verification

After the perfect matching between CBCT and planning CT image of Anthropomorphic RANDO® phantom, it was set as the reference, the known couch shifted was applied and the image registration software was used to determine the position differences. This process was the image registration software verification. The known couch shifted in each axis of lateral (X), longitudinal (Y), and vertical (Z) for both positive and negative directions were varied from 1, 3, 5, 10, 15 and 20 mm. The small deviation from image registration software was found with the maximum error of only 0.3 mm as shown in table 4.1.

Table 4.1 The known shifted values related with actual shifted detected

Known shifted value (mm)	Actual shifted (mm)			Known shifted value (mm)	Actual shifted (mm)		
	Lateral (X)	Longitudinal (Y)	Vertical (Z)		Lateral (X)	Longitudinal (Y)	Vertical (Z)
-1.0	-0.9	-1.0	-0.7	1.0	1.3	1.3	0.7
-3.0	-3.2	-3.0	-3.2	3.0	3.2	2.8	3.2
-5.0	-5.3	-5.0	-5.2	5.0	4.7	4.7	5.2
-10.0	-10.1	-10.1	-9.9	10.0	10.0	10.0	10.3
-15.0	-15.2	-14.7	-15.1	15.0	15.3	15.2	15.0
-20.0	-20.1	-20.1	-20.1	20.0	19.9	19.8	20.1

4.2 Clinical application of image system

Daily treatment, daily CBCT were performed for all patients to verify the area of treated position. From seven selected patients who already finished the course of prostate cancer treatment with VMAT technique, there were totally of 299 CBCT images data set to be analyzed. The results were presented in percentage volume

difference of CTV at $V_{100\%}$, PTV at $V_{95\%}$, bladder and rectum at V_{75Gy}, V_{70Gy}, V_{65Gy}, and V_{60Gy}.

4.2.1 CTV coverage

The absolute volumes of CTV at volume received 100% dose prescriptions ($V_{100\%}$) on planning CT and average of absolute volumes of CTV at $V_{100\%}$ on daily CBCTs for seven patients are presented in table 4.2. The average volume of CTV at $V_{100\%}$ on planning CT was 49.6 ± 11.2 cm^3, while average volume of CTV at $V_{100\%}$ on daily CBCT for all patients was 48.0 ± 13.9 cm^3. The percentage of volume differences that compared at the dose between planning CT and CBCT of each case were within 2.0% except case number 1, however, the volume difference on average from all 7 patients was only -0.1 ± 3.6%.

Table 4.2 The CTV volume from planning CT and all CBCT images at $V_{100\%}$

Patient No.	Planning CT (cm^3)	Average daily CBCT (cm^3)	Volume Difference (%)	P-value
1	56.9	58.7 ± 3.1	4.7 ± 5.5	< 0.01
2	54.8	54.2 ± 1.2	-1.1 ± 2.1	< 0.01
3	63.9	63.4 ± 2.5	-0.7 ± 3.4	0.23
4	54.3	55.1 ± 0.8	-0.6 ± 1.4	0.01
5	45.9	45.7 ± 0.3	-0.5 ± 0.7	< 0.01
6	31.0	30.8 ± 0.6	-0.5 ± 1.8	0.08
7	40.4	39.6 ± 1.0	-2.0 ± 2.5	< 0.01
Mean ± SD	49.6 ± 11.2	48.0 ± 13.9	-0.1 ± 3.6	

The box plot on figure 4.2 shows the percent volume difference data of CTV at $V_{100\%}$ for each patient, which consists of median, lower-, and upper-quartile range and the whiskers of outliers. The outliers represented the percent volume difference data higher than 1.5 times of the lower (Q1) and upper-quartile (Q3).

The results of the box plot of CTV at $V_{100\%}$ for 7 patients were small difference and small variation for all cases. The outliers of data were repersented volumetric error in each fraction. Nevertheless, in some case, the maximum of percentage of

volume difference was 19.1% or 11 cm^3 higher than planning CT for patient number 1.

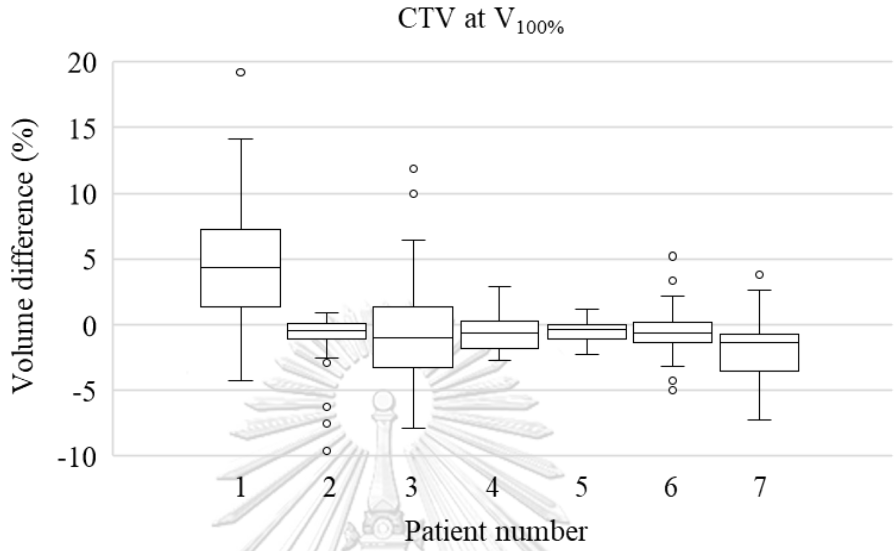


Figure 4.2 Variations in CTV volume differences between daily CBCT and planning CT at $V_{100\%}$ for 7 patients

4.2.2 PTV coverage

The PTV volume coverages at 95% of prescribed dose ($V_{95\%}$) on the daily CBCT compared with planning CT are shown in table 4.3.

Table 4.3 The PTV volume from planning CT and all CBCT images at $V_{95\%}$

Patient No.	Planning CT (cm^3)	Average of daily CBCT (cm^3)	Volume Difference (%)	P-value
1	160.7	152.7 ± 5.8	-5.0 ± 3.6	< 0.01
2	164.3	154.5 ± 2.6	-6.0 ± 1.6	< 0.01
3	177.2	154.9 ± 10.3	-12.6 ± 5.8	< 0.01
4	171.6	160.7 ± 4.0	-6.4 ± 2.3	< 0.01
5	125.0	122.6 ± 3.2	-1.9 ± 2.6	< 0.01
6	94.8	92.2 ± 3.2	-2.8 ± 3.3	< 0.01
7	118.2	104.0 ± 5.1	-12.0 ± 4.3	< 0.01
Mean ± SD	144.5 ± 31.6	130.0 ± 35.4	-6.7 ± 5.3	

The averages $V_{95\%}$ of PTV volume from all 7 cases were 144.5 ± 31.6 cm^3 and 130.0 ± 35.4 cm^3 for planning CT and daily CBCT, respectively. The average of percent volume of difference at $V_{95\%}$ of PTV from all patients was -6.7 ± 5.3%. The maximum $V_{95\%}$ of PTV volume difference was -12.6 ± 5.8% in case number 3.

The box plot of percent volume differences of PTV at $V_{95\%}$ for 7 cases are shown in figure 4.3. The volumes of PTV that received the 95% prescription dose for all patients were lesser than planning CT for all patients. The maximum of volume difference of PTV at $V_{95\%}$ was -27.1% in patient number 3.

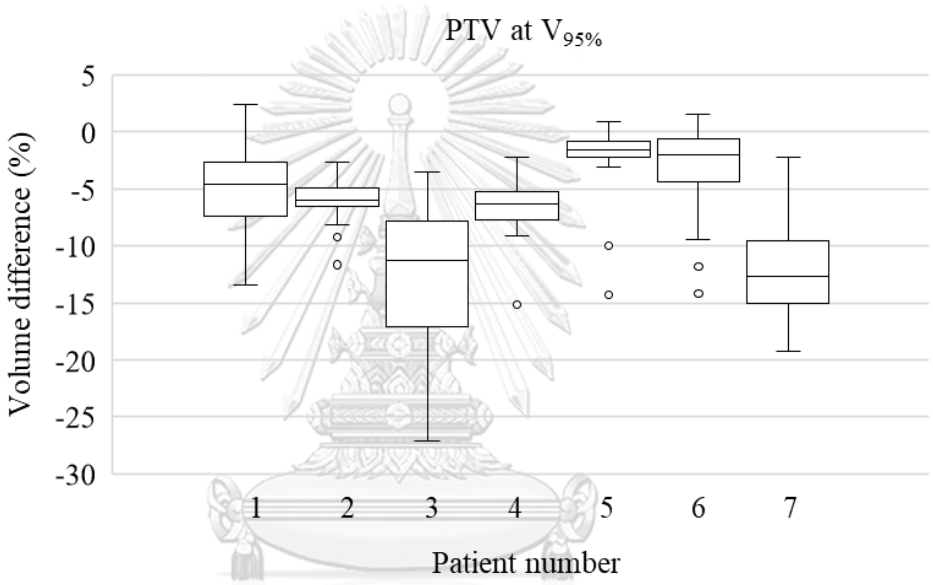


Figure 4.3 Variations in PTV volume differences between daily CBCT and planning CT at $V_{95\%}$ for 7 patients

4.2.3 Bladder volume data

Table 4.4 is the total bladder volume data from planning CT and 299 daily CBCTs in each patient. It was found that the full bladder volumes from daily CBCT were large variation from day-by-day, even the full bladder protocol was performed. However, these variations include in the limitation of CBCT scan length that cannot cover the whole bladder volume in some cases and some sessions.

Table 4.4 The absolute bladder volume data from planning CT and daily CBCT

Patient No.	Bladder Volume (cm^3)		
	Planning CT	Mean ± SD CBCT	
1	701.7	366.2 ± 108.8	(219.9 to 654.7)
2	504.7	392.0 ± 49.4	(298.7 to 487.7)
3	301.0	217.3 ± 59.8	(265.3 to 436.5)
4	527.1	379.6 ± 67.8	(73.4 to 473.4)
5	219.1	191.2 ± 55.8	(92.9 to 278.0)
6	142.9	235.2 ± 84.0	(265.3 to 386.6)
7	306.6	385.9 ± 98.5	(227.6 to 566.4)

A comparison of the bladder dose at high dose area of $V_{75Gy,}$ V_{70Gy}, V_{65Gy} and V_{60Gy} parameters on daily CBCTs and planning CT is presented in table 4.5, 4.6, 4.7, 4.8, respectively.

Table 4.5 shows the bladder volume comparison at V_{75Gy} between using daily CBCT and planning CT. The average difference from all 7 patients was -25.7 ± 25.2%.

Table 4.5 The bladder volume from planning CT and all CBCT images at V_{75Gy}

Patient No.	Planning CT (cm^3)	Average daily CBCT (cm^3)	Volume Difference (%)	P-value
1	32.5	24.6 ± 8.1	-24.3 ± 24.9	< 0.01
2	33.5	32.9 ± 6.0	-1.8 ± 17.8	0.13
3	35.9	21.4 ± 10.0	-40.3 ± 27.8	< 0.01
4	28.9	20.8 ± 4.0	-28.1 ± 13.7	< 0.01
5	6.3	4.6 ± 1.7	-26.9 ± 27.2	< 0.01
6	18.4	14.4 ± 4.3	-20.3 ± 23.4	< 0.01
7	23.4	14.7 ± 4.6	-37.1 ± 19.6	< 0.01
Mean ± SD	25.9 ± 10.5	18.4 ± 10.7	-25.7 ± 25.2	

Patient number 3 showed the largest volume difference of -40.3 ± 27.8%. The results of the bladder volume that received 75 Gy of CBCTs were lesser than planning CT and the bladder volumes from daily CBCT showed very large deviations on day-to-day treatment.

The bladder volume from planning CT at V_{70Gy} was represented the volume that was not exceed dose consideration following by RTOG 0815. The results were the same trend from the results of V_{75Gy} data. The average of daily CBCT at V_{70Gy} showed lesser than the value on planning CT. The average bladder volume difference at V_{70Gy} from planning and actual treatment for seven patients was -24.0 ± 23.2% as presented in table 4.6.

Table 4.6 The bladder volume from planning CT and all CBCT images at V_{70Gy}

Patient No.	Planning CT (cm^3)	Average of daily CBCT (cm^3)	Volume Difference (%)	P-value
1	46.0	37.9 ± 9.4	-18.0 ± 20.5	< 0.01
2	39.9	38.7 ± 6.2	-3.1 ± 15.8	0.06
3	41.6	25.3 ± 11.0	-40.0 ± 26.0	< 0.01
4	34.0	25.6 ± 4.6	-25.1 ± 13.0	< 0.01
5	7.8	5.8 ± 2.0	-26.2 ± 25.4	< 0.01
6	21.5	17.2 ± 4.6	-20.7 ± 21.4	< 0.01
7	27.2	17.8 ± 5.1	-35.5 ± 18.1	< 0.01
Mean ± SD	31.1 ± 13.3	23.0 ± 13.3	-24.0 ± 23.2	

The average volume difference of bladder at V_{65Gy} between daily CBCT and planning CT from all seven patients was -22.8 ± 21.9% as presented in table 4.7, while the average difference of bladder volume at V_{60Gy} was -22.0 ± 20.9% as shown in table 4.8. The volumes detected from daily CBCT were also significantly lesser than the results from planning CT.

Table 4.7 The bladder volume from planning CT and all CBCT images at V_{65Gy}

Patient No.	Planning CT (cm^3)	Average daily CBCT (cm^3)	Volume Difference (%)	P-value
1	64.1	55.3 ± 10.4	-13.7 ± 16.3	< 0.01
2	45.2	43.4 ± 6.6	-4.0 ± 14.6	0.03
3	47.6	28.5 ± 11.6	-40.1 ± 24.3	< 0.01
4	38.9	30.0 ± 4.8	-22.9 ± 12.4	< 0.01
5	9.3	7.0 ± 2.3	-24.7 ± 24.7	< 0.01
6	24.6	19.7 ± 4.9	-18.9 ± 20.2	< 0.01
7	31.1	20.4 ± 5.2	-34.2 ± 16.9	< 0.01
Mean ± SD	37.2 ± 17.6	28.1 ± 17.0	-22.8 ± 21.9	

Table 4.8 The bladder volume from planning CT and all CBCT images at V_{60Gy}

Patient No.	Planning CT (cm^3)	Average of daily CBCT (cm^3)	Volume Difference (%)	P-value
1	86.2	76.3 ± 11.4	-11.5 ± 13.2	< 0.01
2	50.5	48.1 ± 6.8	-4.8 ± 13.5	0.02
3	54.3	32.4 ± 12.4	-40.3 ± 22.7	< 0.01
4	44.4	35.1 ± 5.2	-21.0 ± 11.8	< 0.01
5	11.0	8.4 ± 2.7	-23.7 ± 24.5	< 0.01
6	28.0	22.8 ± 5.2	-19.3 ± 18.9	< 0.01
7	35.3	23.6 ± 5.6	-33.3 ± 15.8	< 0.01
Mean ± SD	44.2 ± 23.6	33.9 ± 22.2	-22.0 ± 20.9	

From all of bladder parameters, patient number 3 presented the largest volume and variation from day-to-day during treatment course as seen in daily CBCT data and also showed the largest bladder volume difference between daily CBCT and planning CT.

The box plot for variations of bladder volume at V_{75Gy}, V_{70Gy}, V_{65Gy} and V_{60Gy} for seven cases are shown in figure 4.4, 4.5, 4.6, 4.7, respectively.

Figure 4.4 shows the maximum volume difference of bladder volume at V_{75Gy} of -95.3% in patient number 5 representing the lesser dose at V_{75Gy} than planning CT.

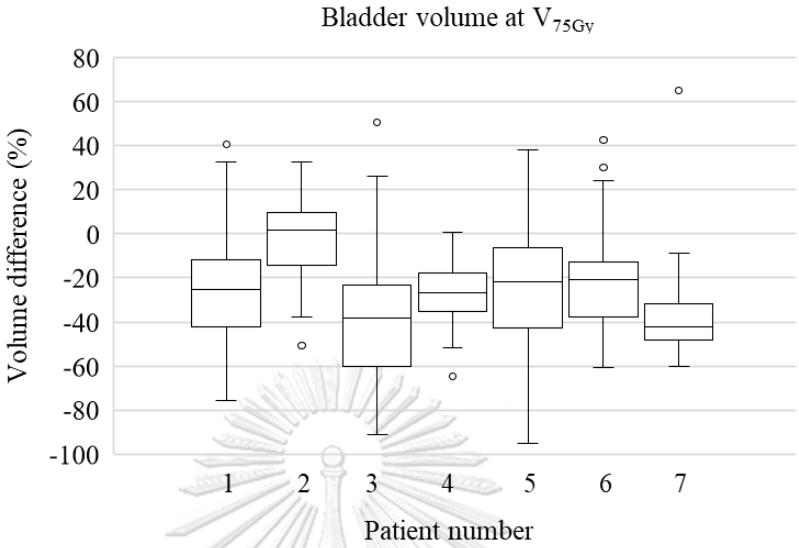


Figure 4.4 Variations in the bladder volume at V_{75Gy} for 7 patients

Figure 4.5 shows the maximum volume difference of bladder volume at V_{70Gy} of -94.3% for patient number 5, while figure 4.6 shows the maximum volume difference of bladder volume at V_{65Gy} of -92.8% for patient number 5.

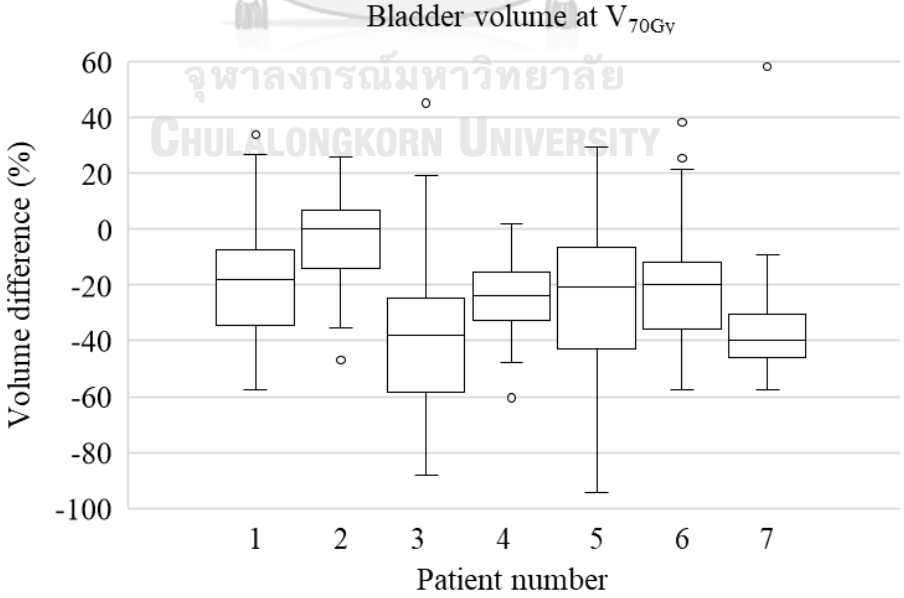


Figure 4.5 Variations in the bladder volume at V_{70Gy} for 7 patients

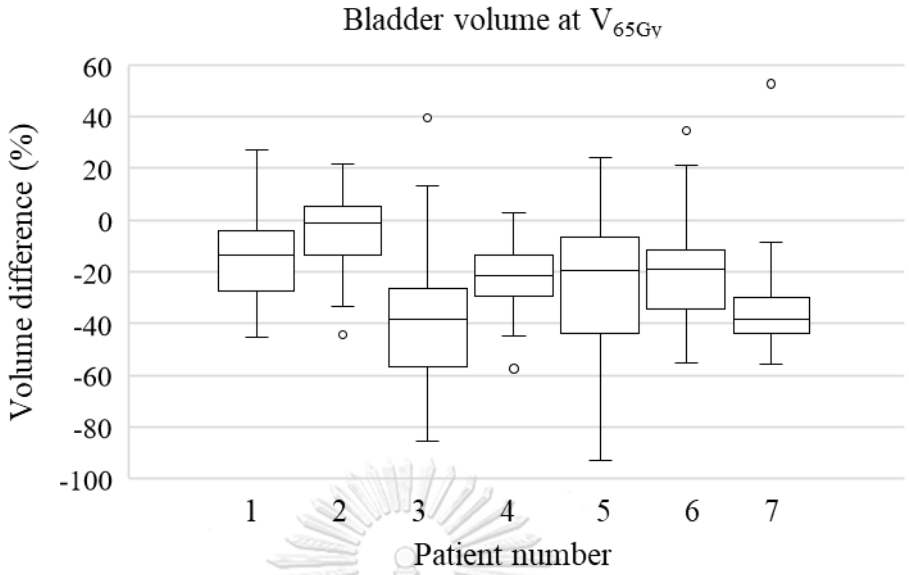


Figure 4.6 Variations in the bladder volume at V_{65Gy} for 7 patients

The variations in the bladder volume at V_{60Gy} for 7 patients are shown in figure 4.7. The box plot shows the maximum volume difference of bladder volume at V_{60Gy} of -99.8% for patient number 5.

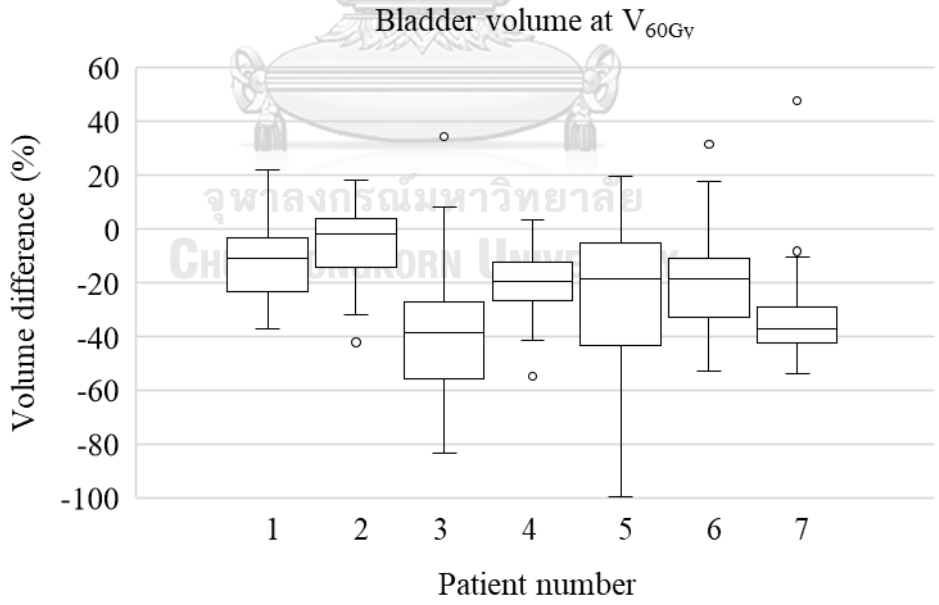


Figure 4.7 Variations in the bladder volume at V_{60Gy} for 7 patients

4.2.4 Rectum volume data

The total rectum volume data consisted of planning CT and 299 daily CBCTs in each patient. The total of rectum volume of daily CBCTs were varied from 29.5 cm^3 to 153.4 cm^3 as displayed in table 4.9. The rectum volumes from daily CBCT were large variation, however, these variations include in the limitation of patient preparation. The rectum dose at high dose area of $V_{75Gy,}$ V_{70Gy}, V_{65Gy} and V_{60Gy} parameters on daily CBCTs and planning CT were compared as shown in table 4.10, 4.11, 4.12, 4.13, respectively.

Table 4.9 The absolute rectum volume data from planning CT and daily CBCT

Patient No.	Rectum Volume (cm^3)		
	Planning CT	Mean ± SD CBCT	
1	69.6	66.5 ± 22.6	(37.5 to 153.4)
2	64.3	49.6 ± 8.5	(40.0 to 80.0)
3	56.9	75.6 ± 20.4	(46.6 to 127.5)
4	42.7	36.8 ± 8.1	(27.2 to 68.6)
5	41.1	43.6 ± 7.8	(5.4 to 65.4)
6	40.2	51.6 ± 8.8	(7.6 to 70.3)
7	42.0	38.6 ± 5.9	(31.9 to 59.8)

The average difference from all 7 patients was 22.3 ± 74.6%. The maximum volumes difference at V_{75Gy} was up to 90.1% ± 52.9% for patient number 7 as shown in table 4.10.

Table 4.10 The rectum volume from planning CT and all CBCT images at V_{75Gy}

Patient No.	Planning CT (cm^3)	Average daily CBCT (cm^3)	Volume Difference (%)	P-value
1	10.4	10.6 ± 7.8	1.4 ± 74.3	0.91
2	11.1	5.8 ± 2.5	-48.1 ± 22.7	< 0.01
3	10.6	13.1 ± 7.1	23.5 ± 67.2	0.02
4	5.2	4.0 ± 2.8	-21.7 ± 54.7	0.03
5	5.0	8.6 ± 3.5	72.1 ± 69.6	< 0.01
6	5.9	8.2 ± 3.5	39.6 ± 60.1	< 0.01
7	6.1	11.6 ± 3.2	90.1 ± 52.9	< 0.01
Mean ± SD	7.7 ± 2.8	8.6 ± 3.7	22.3 ± 74.6	

The average volume difference of rectum at V_{70Gy} between daily CBCT and planning CT from all seven patients was 16.9 ± 60.8% as presented in table 4.11, while the average difference of rectum volume at V_{65Gy} was 14.2 ± 52.4% as shown in table 4.12. The volumes detected from daily CBCT were also significantly larger than the results from planning CT.

Table 4.11 The rectum volume from planning CT and all CBCT images at V_{70Gy}

Patient No.	Planning CT (cm^3)	Average daily CBCT (cm^3)	Volume Difference (%)	P-value
1	14.3	14.1 ± 8.6	-1.0 ± 60.2	0.92
2	13.6	8.0 ± 2.8	-41.2 ± 20.5	< 0.01
3	12.9	15.4 ± 7.3	18.8 ± 56.2	0.03
4	7.1	6.0 ± 3.3	-15.9 ± 46.4	0.06
5	7.0	10.7 ± 3.8	53.4 ± 53.6	< 0.01
6	7.6	10.2 ± 3.9	33.3 ± 51.3	< 0.01
7	7.5	12.9 ± 3.4	71.7 ± 44.9	< 0.01
Mean ± SD	10.0 ± 3.4	10.7 ± 6.2	16.9 ± 60.8	

Table 4.12 The rectum volume from planning CT and all CBCT images at V_{65Gy}

Patient No.	Planning CT (cm^3)	Average daily CBCT (cm^3)	Volume Difference (%)	P-value
1	18.1	17.7 ± 9.3	-1.9 ± 51.3	0.80
2	15.6	9.8 ± 3.0	-37.0 ± 18.9	< 0.01
3	14.9	17.4 ± 7.4	16.7 ± 49.4	0.03
4	8.6	7.7 ± 3.6	-11.2 ± 42.6	0.07
5	8.9	12.6 ± 3.9	43.4 ± 44.4	< 0.01
6	9.1	12.0 ± 4.2	30.5 ± 46.4	< 0.01
7	8.8	14.1 ± 3.5	59.3 ± 39.5	< 0.01
Mean ± SD	12.0 ± 4.0	13.1 ± 6.7	14.4 ± 52.4	

The average volume difference of rectum at V_{60Gy} between daily CBCT and planning CT from all seven patients was 11.9 ± 46.6% as displayed in table 4.13.

Table 4.13 The rectum volume from planning CT and all CBCT images at V_{60Gy}

Patient No.	Planning CT (cm^3)	Average of daily CBCT (cm^3)	Volume Difference (%)	P-value
1	22.3	21.8 ± 9.9	-2.3 ± 44.5	0.74
2	17.5	11.6 ± 3.1	-33.9 ± 17.6	< 0.01
3	16.8	19.3 ± 7.5	14.5 ± 44.4	0.04
4	10.2	9.2 ± 3.8	-9.3 ± 37.7	0.19
5	10.8	14.8 ± 4.1	36.9 ± 38.0	< 0.01
6	10.6	13.6 ± 4.6	28.5 ± 43.2	< 0.01
7	10.1	15.2 ± 3.6	50.6 ± 35.4	< 0.01
Mean ± SD	14.1 ± 4.8	14.6 ± 7.3	11.9 ± 46.6	

The box plot of the variations of rectum at V_{75Gy}, V_{70Gy}, V_{65Gy} and V_{60Gy} for seven cases is shown in figure 4.8, 4.9, 4.10, 4.11, respectively. It was found that the variation in rectum volume at V_{75Gy}, V_{70Gy}, V_{65Gy}, and V_{60Gy} for all patients showed the large variation especially patient number 7 that presented the average volume difference up to 90.1% as presented in figure 4.8. The maximum volume difference of rectum volume at V_{75Gy} was up to 352.9% on patient number 5.

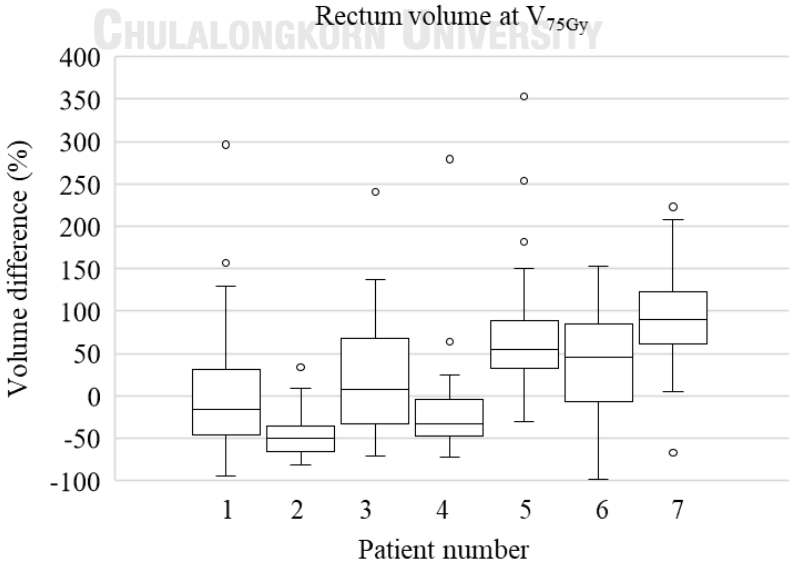


Figure 4.8. Variations in the rectum volume at V_{75Gy} for 7 patients

Figure 4.9 shows the maximum volume difference of rectum volume at V_{70Gy} of 268.3% for patient number 5, while the maximum volume difference of rectum volume at V_{65Gy} was 222.0%. We found that most of the rectum volumes of planning CT were lesser than CBCT as displayed in figure 4.10.

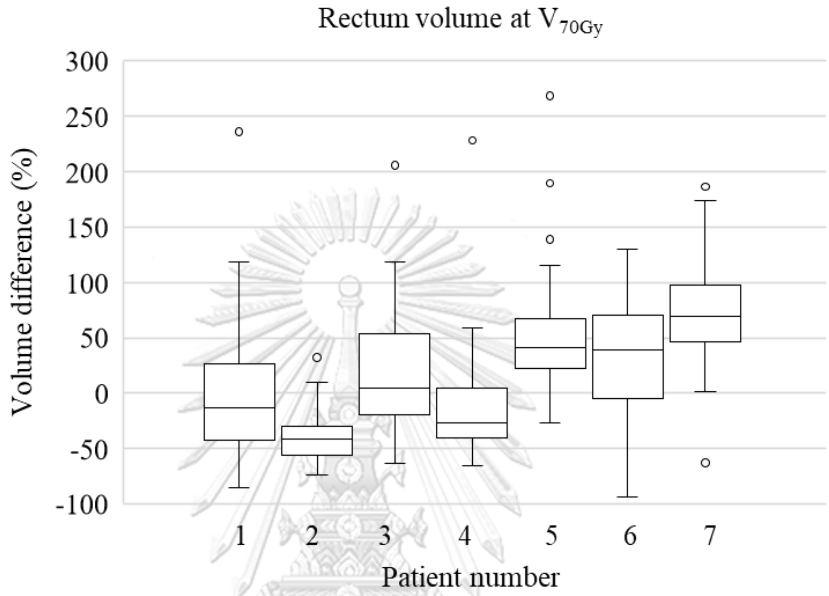


Figure 4.9 Variations in the rectum volume at V_{70Gy} for 7 patients

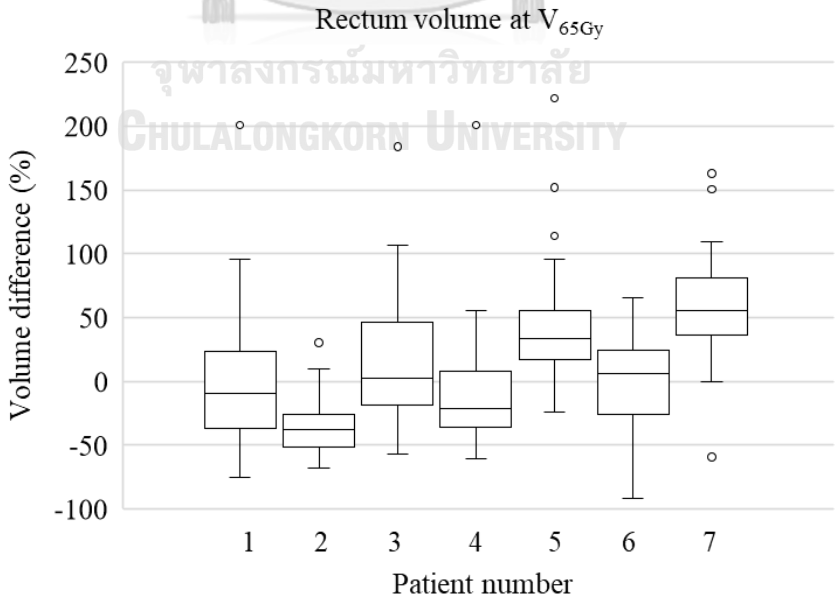


Figure 4.10 Variations in the rectum volume at V_{65Gy} for 7 patients

Figure 4.11 shows the rectum volume difference between planning and CBCT within 200% for all patients. However, the trend of rectum volume was higher in CBCT than planning CT.

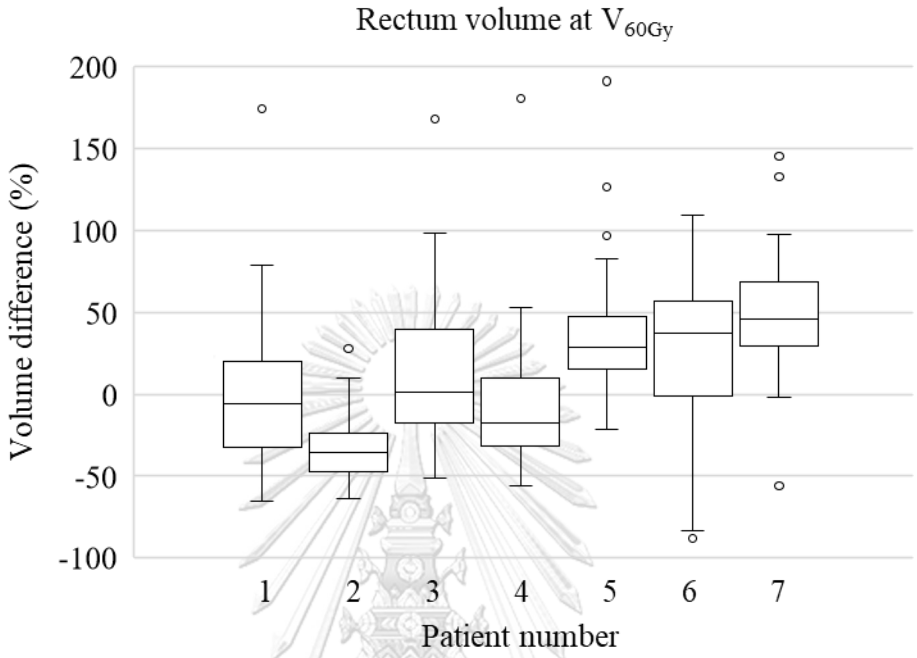


Figure 4.11 Variations in the rectum volume at V_{60Gy} for 7 patients

CHAPTER V
DISCUSSION AND CONCLUSION

5.1 Discussion

5.1.1 HU and electron density verification

The Catphan® 600 phantom is commonly used for image quality control and assessment of both CT scanner and CBCT. The section 2 of the Catphan® 600 phantom (CTP404) can also be used to evaluate the HU and electron density relationship because it consists of various materials. The HU from CBCT should be the same value as the value from CT simulator to confirm that the HU and electron density relationship curve from CT can be applied to CBCT image for dose calculation. The Catphan® 600 phantom was scanned with 120 kVp for CT simulator and 125 kVp for CBCT on pelvis protocol as the routine scanning. The relative of electron density, the relationship between electron density of any materials divided by electron density of water, were plotted on the graph with HU values in both imaging modalities. The HU differences were analyzed because this difference is possible to impact on dose calculation for treatment planning. From the results, the HU values in low density objects (relative electron density between 0 and 1.5) were not significantly different, while high density object with the relative electron density more than 1.5 were significantly different. The maximum difference was up to 108 HU or 12% at Teflon material. Skrzyński W, et al [20] reported that the HU-ρ_e relationships predefined in TPS can be used for general-purpose CT systems operating at voltages close to 120 kVp (120 to 140 kVp). The CBCT should be measured and carefully analyzed before using CT data for treatment planning. Our results agree with the results from Yoo S, et al [14] whom presented the small HU difference between CT and CBCT of Catphan except Teflon. Thus, the HU curve of CT simulation image that was commissioned in treatment planning is possible to apply for recalculation on CBCT images. However, the HU value depends on kV setting and vary dramatically between scanners and imaging protocols. Several studies reported the impact of kVp to HU value and dose calculation. Cozzi L, et al [21] reported that voltage variation from 100 kVp to 140 kVp caused a maximum of

300 HU difference in high-density materials that resulted in 4% dosimetric error. This part can be concluded that using 125 kVp CBCT image instead of 120 kVp in planning CT image would not produce considerable variations. The limitations of this method were the limited number of electron density materials in phantom that were a lot of lesser than the electron densities in patient, and also the shape and size of phantom were different from the shape of patient. Moreover, the image quality of CBCT was lesser than planning CT due to high scatter dose in field of CBCT beam. This problem affects to the more difficulty on organ contouring in CBCT.

5.1.2 Dose verification

Besides the HU value, another issue that should be considered was the dose calculation on CBCT and CT images with the same electron density relationship curve. The same simple plan on CBCT and planning CT image of Anthropomorphic RANDO® phantom were calculated to determine the effect of using CBCT image for dose calculation. The gamma passing rate was used to evaluate the 2D central axis plane differences. We observed the perfect match of 100% gamma passing rate when 3%/3mm and 2%/2mm gamma criteria were used. Even the very strict criteria of 1%/1mm gamma criteria was set, the passing rate was still higher than 95%. These results could be confirmed that CBCT images were possible to apply for accurate dose calculation. The accuracy of dose calculation from CBCT was the results of the same CT number between these the image set from the previous part. The result was consistent with Yoo S, et al [14] they reported that CBCT-based treatment plans were dosimetrically comparable to CT-based treatment plans.

5.1.3 Image registration verification

The image registration was important process that was used to confirm the accuracy of patient positioning. This image registration software was verified by comparing the registration results with known shifted values. The known shifted values were adapted from the movement of the treatment couch that already passed the mechanical quality control. After the simulated couch shifted in various values, the registration results showed the differences lesser that 1.0 mm for all X, Y, and Z directions and both positive and negative sides. The average error was 0.1 mm with

the most highest error in lateral direction. This is might be due to the first setup error, however this error was within ± 1.0 mm limitation.

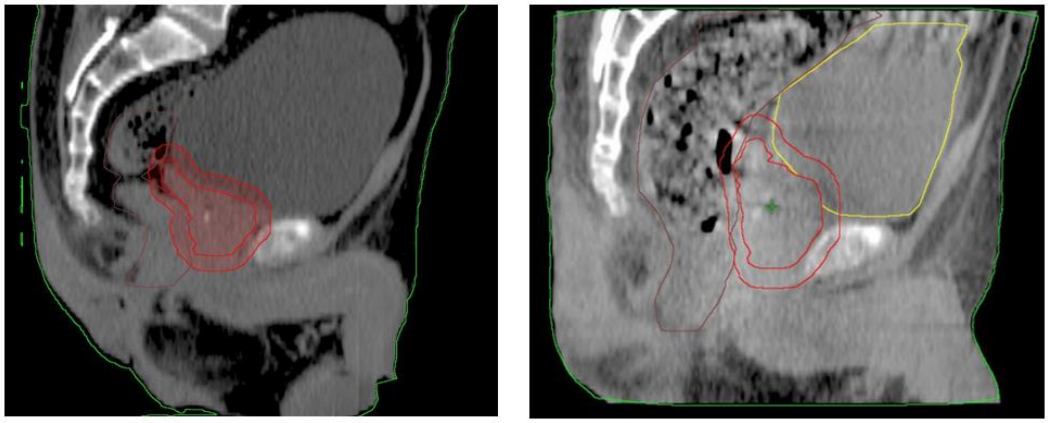
The limitation of this step is the rigid transformation software that can be moved in only translation and rotation. The results were good in Anthropomorphic RANDO® phantom as the static phantom and fixed organ. In clinical situation, however, the organs inside the body always move and change during the course of treatment. The non-rigid image registration software is preferred.

5.1.4 Daily dosimetric difference in clinical part

The original treatment planning process used planning CT image to calculate the dose distribution and evaluated the dose to target and surrounding critical organs. During treatment, the CBCT was performed to verify the patient setup error. It is not only the patient setup error presented on CBCT images, but the organs inside body were also changed. The daily CBCT images were applied for dose calculation to evaluate the actual dose that patient received during the course of treatment. The original plans on planning CT were transferred to recalculate on daily CBCT with the actual organ positions. In clinical situation, the full bladder and empty rectum protocols were recommended for patient preparation during radiotherapy treatment to control the position of organs that represented to the same dose during treatment as the dose at planning CT.

From the results, the daily CTV dose at $V_{100\%}$ was the same as CTV dose at planning CT with the differences lesser than 2% except case number 1. It can be concluded that the CTV to PTV margin was enough to compensate all of the possible uncertainties including bladder and rectum filling variation during course of prostate cancer treatment. The largest CTV at $V_{100\%}$ difference at patient number 1 was 4.7 ± 5.5% (1.8 cm^3 on average). This difference represented the change of prostate gland due to the large variation of bladder and rectum volume as shown in figure 5.1.

The change of CTV may cause the reducing of disease control and enhance normal tissue complication for patient.



(A) (B)

Figure 5.1 (A) CT simulation image and (B) CBCT image

The image quality was another factor that has an effect to the CTV contouring. CBCT images certainly included higher scatter radiation dose in the field and made the results in poorer image quality than CT images.

The PTV is extended the margin from contoured CTV according to RTOG 0815 protocol. The CTV to PTV margins were added to take into account all the uncertainties in planning, patient positioning and beam positioning. The PTV volumes were 8 mm margin expanded from CTV for all direction except posterior that used 5 mm for reducing the effect of rectum doses. As the results, we found that the PTV at $V_{95\%}$ for all patients showed the average of all CBCTs lesser than planning CT.

The percent volume difference between daily CBCT and planning CT represented to the dose differences of the organs. The bladder and rectum volumes changed during the course of treatment affected to dose received of those organs including the shape and dose on CTV and PTV. The percent volume difference was -23.6 ± 22.8% for bladder while the rectum volume differences was 16.4 ± 58.6%. The bladder volumes at high dose region during treatment were significantly smaller than the volumes during planning that showed in minus high value. The maximum and minimum bladder volume differences in high dose area were -87.92% and 1.36%, respectively. These large differences were mainly due to the different full bladder volume and empty rectum protocol during CT planning scanned and CBCT before the course of treatment. Before CT simulation process, the patients had to prepare NPO before CT simulation. Some patients required to have normal saline via intravenous injection to

received full bladder. It would be difficult to have the actual full bladder. The patient sensation of full bladder during planning CT scanned and CBCT scanned may not be the same. This is the different process of full bladder during treatment. The high dose area of rectum volume during the course of treatment showed very small average difference but presented very large deviation. The deviation of rectum volume was due to the difficultly to clear the daily empty rectum of patient. For rectum volume, the largest average volume difference of daily CBCT was up to 90.1% at V_{75Gy} and 70.7% at V_{70Gy} that represented 5.5 cm^3 in the absolute volume. This largest average volume difference was approximately about one of quarter lower than Pearson D, et al [15] who found the largest average volume difference rectum at V_{70Gy} of rectum by 295%. The overall of rectum volume at V_{70Gy} of our study was under the dose limitation of adjacent OARs for prostate cancer radiotherapy according to RTOG 0815 as displayed in figure 5.2.

Figure 5.2 is the dose volume histograms that showed the relationship between normalized volume (%) and absolute dose (cGy) of rectum for 7 patients. A star symbol represents the dose limitation of rectum at V_{70Gy}. The patient number 7 showed the rectum at V_{70Gy} larger than the RTOG 0815 limitation because the rectum area of this case overlaps to PTV in large area. Emami B, et al [22] reported that the population risk of late rectum toxicity was lesser than 10% on grade 2 and 15% on grade 3 late toxicity if $V_{70Gy} < 20\%$. The risk of late rectum toxicity correlated with the rectum volume exposed to high doses and also have impacted on late rectum toxicity.

The averaged rectum volume over the course treatment on daily CBCT

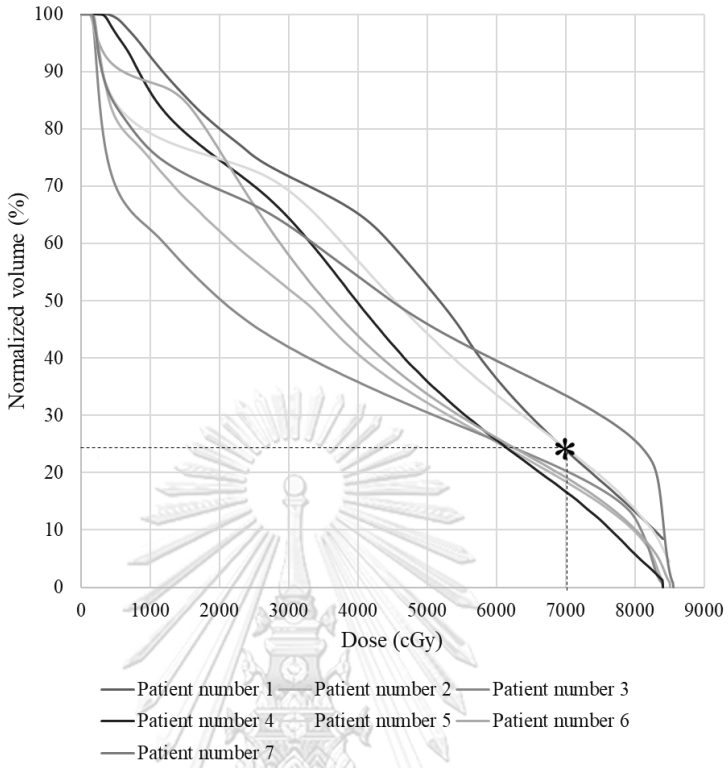


Figure 5.2 The DVHs of normalize volume and dose of rectum volume for 7 patients

In addition, another factor that affected to dose received by these organs was the CBCT verification and protocol of image registration due to various operators. Figure 5.3 shows the CTV on daily CBCT in red line and CTV on planning image in red area. It was found that the rectum volume moved into the high dose region up to 50% of volume.

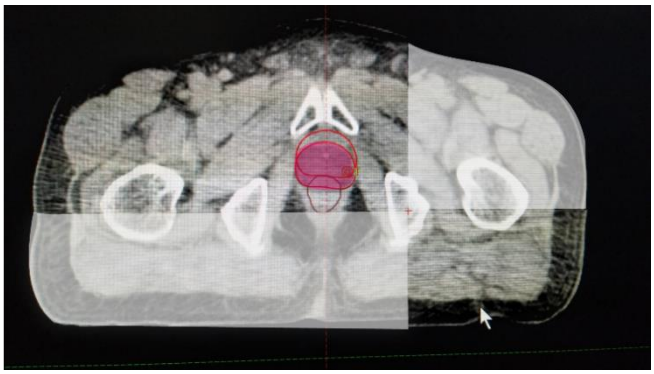


Figure 5.3 The rectum volume on high dose region from daily CBCT

Chen Z, et al [16] reported that the bladder's volume change was more significant than that of the rectum for the prostate cancer patient. This result agreed with our study. Pearson D, et al [15] reported that the bladder and rectum volume changes caused an effect on the cumulative dose of the target and those structures. However, our study showed the small dose difference of the target in actual position compared with planning position, especially for CTV so the CTV to PTV margin was enough expansion.

Although we have the protocol to control bladder and rectum volumes during treatment, these OAR volumes still showed the large variation, especially for bladder volume. These bladder and rectum filling changes were directly affected to the plan dose distribution as shown in the results of percent gamma passing rate lesser then 95% for all cases. Moreover, the V_{70Gy} of both bladder and rectum comparison between planning CT and daily CBCT showed the large difference with 85.3% of time lower volume for bladder and 69.9% of time higher volume for rectum of CBCT plan compared with original planning CT plan. The differences of bladder and rectum volumes were also impacted to $V_{95\%}$ of PTV that showed around 6.7% differences, however, the dose of CTV of daily treatment were still the same as the plan with the differences of $V_{100\%}$ only 0.1%.

5.2 Conclusion

During the course of prostate cancer treatment, organs at risk always daily changes. These changes can be investigated by the dosimetric comparison between the dose on daily CBCT and planning CT images. The dosimetric differences between using daily CBCT and planning CT in volumetric modulated arc therapy technique is not significantly different for CTV, in contrast, the dosimetric differences of the bladder and rectum are quite significant. The bladder and rectum show large difference and variation during the course of treatment. The bladder volume decreases on average of daily CBCT, while the rectum volume increases. As the volume of the bladder decrease, the dose received by the bladder decreases. When the size of rectum increases, so does the rectal dose increase. The bladder and rectum volume difference have affected to dosimetric distribution related to the shape of CTV and PTV, but the dosimetric distribution of CTV still cover on 100% that means the dose differences

are not impacted to dose of CTV received. Moreover, other factors may be impact to dosimetric effect such as CBCT verification, setup position, patient's movement etc. We suggest that the daily CBCT is necessary for prostate cancer radiotherapy, the bladder and rectum volume should be considered and should be carefully validated for treatment verification process.

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APPENDICES

APPENDIX A

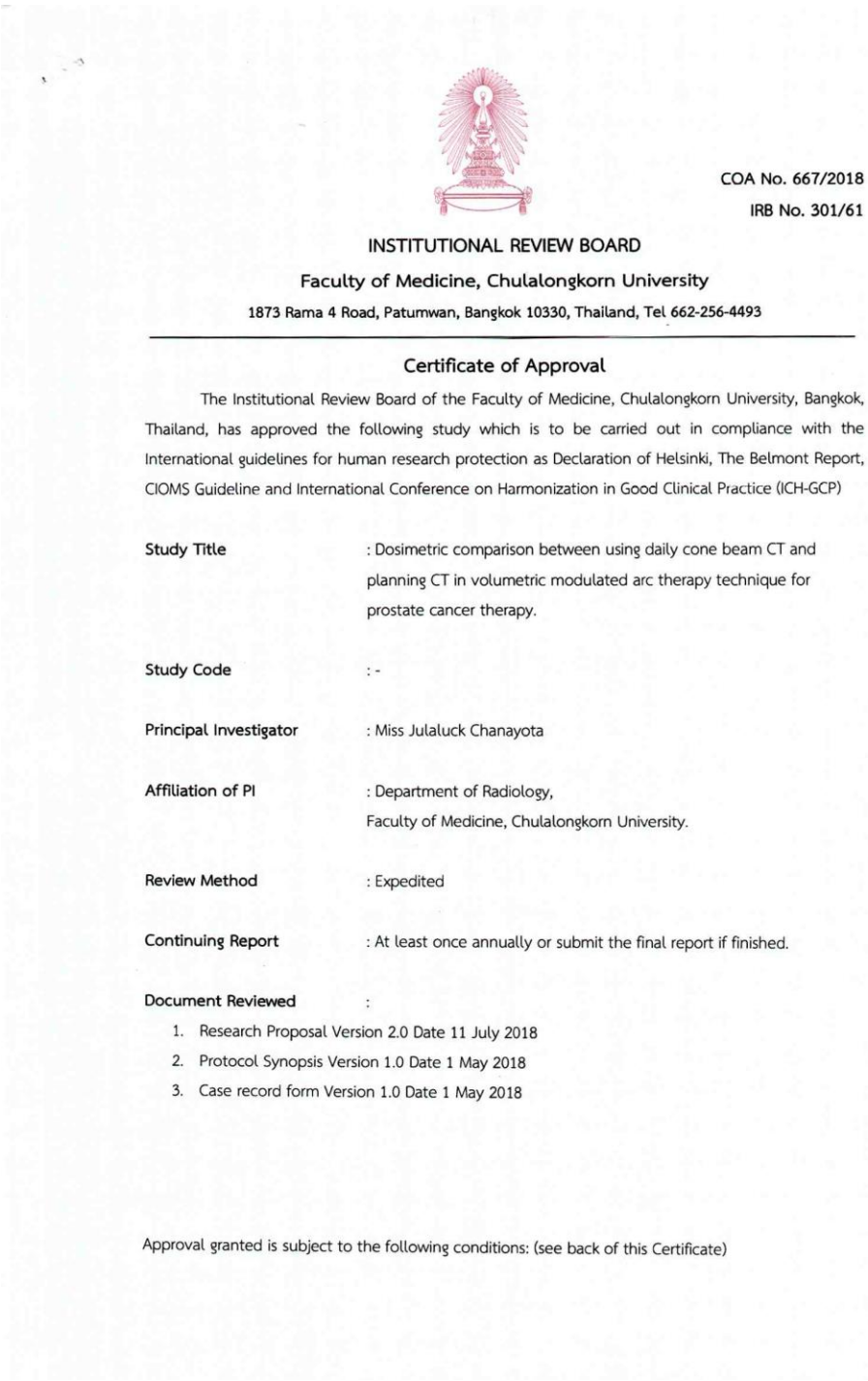
Data record form

Study date: [_____/_____/_____] (dd/mm/yyyy)						
Patient information						
Patient number:						
Treatment information						
CT Simulation date: [_____/_____/_____](dd/mm/yyyy)						
Start RT date: [_____/_____/____] (dd/mm/yyyy)				End RT: [_____/_____/_____](dd/mm/yyyy)		
Dose (Gy)	Bladder volume			Rectum volume		
	Planning CT (cm^3)	Average daily CBCT (cm^3)	Vol. difference (%)	Planning CT (cm^3)	Average daily CBCT (cm^3)	Vol. difference (%)
V_{75}						
V_{70}						
V_{65}						
V_{60}						
CTV volume				PTV volume		
Dose (%)	Planning CT (cm^3)	Average daily CBCT (cm^3)	Vol. difference (%)	Planning CT (cm^3)	Average daily CBCT (cm^3)	Vol. difference (%)
V_{100}						
V_{95}						
CBCT Information						
CBCT No. date: [_____/_____/_____] (dd/mm/yyyy)						
Dose (Gy)	Bladder volume (cm^3)			Rectum volume (cm^3)		
V_{75}						
V_{70}						
V_{65}						
V_{60}						
Dose (%)	CTV volume (cm^3)			PTV volume (cm^3)		
V_{100}						
V_{95}						

APPENDIX B

The approval of institutional review board

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



COA No. 667/2018
IRB No. 301/61

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

Certificate of Approval

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 comparison between using daily cone beam CT and planning CT in volumetric modulated arc therapy technique for prostate cancer therapy.

Study Code : -

Principal Investigator : Miss Julaluck Chanayota

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

Review Method : Expedited

Continuing Report : At least once annually or submit the final report if finished.

Document Reviewed :

1. Research Proposal Version 2.0 Date 11 July 2018
2. Protocol Synopsis Version 1.0 Date 1 May 2018
3. Case record form Version 1.0 Date 1 May 2018

Approval granted is subject to the following conditions: (see back of this Certificate)

VITA

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PUBLICATION	Chanayota, Julaluck, et al. "Dosimetric effect on daily bladder and rectum fillings during course of prostate cancer treatment in Volumetric Modulated Arc Therapy technique." Medical Physics for Patient Benefit (2019): 97.