Kaunas University of Technology

Faculty of Mathematics and Natural Sciences

Analysis of Dosimetric Variation due to the Bladder and Rectum Volume Changes for the Prostate Cancer Radiotherapy

Master's Final Degree Project

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Kaunas, 2022

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Summary

Prostate cancer is one of the most common forms of cancer among men. Radiation therapy is often used to treat prostate cancer. The prostate is a moving organ, but its locations can also be affected by the nearby bladder and rectum, whose volumes are always changing. For this reason, in order to estimate the changing organ volumes in radiotherapy before each therapeutic fraction could be used one of the image-guided radiotherapy techniques, for example, cone-beam computed tomography (CBCT). CBCT is an important part of radiotherapy. This helps to assess the localisation of the targets of the prescribed treatment, allows for the adjustment of treatment plans, if necessary, reduces errors and improves the detection of moving organs. CBCT has two energy types – megavoltage and kilovoltage. It consists of a megavoltage and kilovoltage "source" and detector.

In the final degree project, were used a linear accelerator *Halcyon* system with an integrated kV-CBCT imaging technique, for patient scanning was selected protocol called *Pelvis*. Images of the patient were transferred to the treatment planning system (TPS) *Eclipse*, where the bladder and rectum re-contouring and treatment planning on daily kV-iCBCT images were performed, analysing irradiation doses and volume changes of these organs, and additionally to the irradiated target volume.

Results of the research were evaluated regarding the daily kV-iCBCT volume values (mean, minimum, and maximum) of bladder and rectum changes for the patients. Two patients were analysed in total. Bladder and rectum volume varied from 64.5 cc to 319.0 cc (Patient 1/ bladder), and from 49.5 cc to 148.3 cc (Patient 1/ rectum), respectively, while for the Patient 2 - 55.4 cc ÷ 298.8 cc (bladder), and 38.2 cc ÷ 107.9 cc (rectum). Dose-volume histograms showed that the changing volumes of organs affect the dose of ionizing radiation. Also, volumes were compared between treatment planning results planned on computed tomography and kV-iCBCT. The final results showed a good agreement for PTV target volumes coverage from 0.00 % to 0.02 % (Patient 1) and from -0.03 to -0.05 % (Patient 2), Boost coverage differed from -0.03 % to -0.07 % (Patient 1) and from -0.01 % to -0.02 % (Patient 2), which means that treatment planning could be successfully performed on daily kV-iCBCT images.

Agnė Giedrytė. Dozimetrinių pokyčių dėl šlapimo pūslės ir tiesiosios žarnos tūrio pokyčių analizė prostatos vėžio radioterapijai. Magistro baigiamasis projektas / vadovė doc. dr. Jurgita Laurikaitienė; Kauno technologijos universitetas, Matematikos ir gamtos mokslų fakultetas.

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Santrauka

Prostatos vėžys yra dažniausiai pasitaikanti vėžio forma tarp vyrų. Spindulinė terapija dažnai skiriama gydyti prostatos vėžiui. Prostata yra natūraliai judantis organas, bet jos lokalizacija gali būti paveikta ir šalia esančios šlapimo pūslės bei tiesiosios žarnos, šių organų tūriai nuolatos kinta. Dėl šios priežasties, vertinant šių organų tūrio pokytį, spindulinėje terapijoje prieš kiekvieną gydymo frakciją, gali būti naudojama vaizdinė radioterapija, pavyzdžiui, kūginio pluošto kompiuterinė tomografija (KPKT). KPKT yra labia svarbi dalis spindulinėje terapijoje. Šis metodas leidžia tiksliai lokalizuoti naviko vietą pagal paskirtą gydymo planą, leidžia koreguoti gydymo planą procedūros eigoje, jei to reikia, sumažina paklaidų skaičių ir pagerina judančių organų aptikimą. KPKT turi dvi energijas – megavoltinę (MV) ir kilovoltinę (kV). Sistema sudaryta is megavoltinio ir kilovoltinio "šaltinio" ir detektoriaus.

Baigiamajame projekte naudotas linijinis greitintuvas *Halcyon* su integruota kV-KPKT vaizdinimo sistema, pacientų skenavimui buvo pasirinktas protokolas *Dubuo*. Gauti paciento vaizdai perkelti į gydymo planavimo sistemą *Eclipse*, kurioje atliktas šlapimo pūslės ir tiesiosios žarnos kontūravimas ir gydymo planavimas ant KPKT vaizdų, analizuojant šių organų apšvitos dozių ir tūrių pokyčius bei papildomai apšvitintą tūrį.

Tyrimo rezultatai buvo įvertinti atsižvelgiant į pacientų šlapimo pūslės ir tiesiosios žarnos kasdieninius tūrio pokyčių reikšmes (vidurkis, mažiausias ir dižiausias). Buvo ištirti du pacientai. Šlapimo pūslės ir tiesiosios žarnos tūris keitėsi nuo 64.3 cm^3 iki 319.0 cm^3 (Pacientas 1/ šlapimo pūslė) ir nuo 49.5 cm^3 iki 148.3 cm^3 (Pacientas 1/ tiesioji žarna) atitinkamai, tuo tarpu Pacientas 2 – 55.4 cm^3 ÷ 298.8 cm^3 (šlapimo pūslė) ir 38.2 cm^3 ÷ 107.9 cm^3 (tiesioji žarna). Dozės tūrio histogramos parodė, kad besikeičiantis organų tūris paveikia jonizuojančios spinduliuotės doze. Taip pat, tūriai buvo palyginti gydymo planavimo rezultatai tarp planavimo atlikto ant kompiuterinės tomogafijos vaizdų ir ant pasikartojančių kūginio pluošto kompiuterinės tomografijos vaizdų. Galutiniai rezultatai parodė gerą tikslinį tūrių pasidengimą reikiama doze tarp pacientų, nuo 0.00 % iki 0.02 % (Pacientas 1) ir nuo -0.03 % iki -0.05 % (Pacientas 2), papildomos dozės pasidengimas svyravo nuo -0.03 % iki -0.07 % (Pacientas 1) ir nuo -0.01 % iki -0.02 % (Pacientas 2), tai reiškia, kad planavimas gali būti sėkmingai atliekamas ant kV-KPKT vaizdų.

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List of abbreviations and terms

Abbreviations:

2D – two-dimensional

3D – three-dimensional

ART – adaptive radiotherapy

CBCT – cone-beam computed tomography

CT – computed tomography

CTV – clinical target volume

DRR – digitally reconstructed radiography

DVH – dose volume histograms

EM – electromagnetic

EPID – electronic portal imaging device

EU – European Union

FBCT – fan beam computed tomography

FFF – flattening filter free

FOV – field of view

FPD – flat panel detector

GTV – gross tumour volume

HT – helical tomotherapy

HU – Hounsfield units

IAEA – International Atomic Energy Agency

iCBCT – iterative cone-beam computed tomography

ICRU – International Commission on Radiation Units and Measurements

IGRT – image-guided radiotherapy

IMRT – intensity-modulated radiation therapy

IR – irradiated volume

kV – kilovoltage

MLC – multi-leaf collimator

MRI – magnetic resonance imaging

MU – monitor unit

MV – megavoltage

NAL – no action level

OAR – organ at risk

OBI – On-Board imaging

PSA – prostate-specific antigen

PTV – planning target volume

RT – radiotherapy

RPM – rotation per minute

RTOG – Radiation Therapy Oncology Group

SAL – shrinking action level

SBRT – stereotactic body radiotherapy

SID – source-to-isocenter distance

TPS – treatment planning system

TV – treated volume

US – ultrasound

VMAT – volumetric modulated arc therapy

WHO – World Health Organisation

Introduction

The prostate cancer accounts for 20% of all cancers in men. It is known that prostate variations of shape could be affected by filling of rectum or bladder, and that could modificate a distribution of irradiation dose in the target and organs at risk (OARs). Due to this reason image-guided radiotherapy (IGRT) is very *important* reducing errors of target localisation, and improvement, and optimisation of irradiation accuracy. It helps to ensure that a proper irradiation dose will reach the target, at the same time minimizing additional radiation to the surrounding tissues. Also, IGRT determines the exact coverage of the target, ensure quality, and safety for the patient in a real time before each treatment procedure. Moreover, IGRT systems are divided into two groups: 1) based on ionising radiation and 2) based on non-ionising radiation. Ionising radiation systems include electronic portal imaging devices, megavoltage and kilovoltage cone-beam computed tomography (CBCT), while non-ionising radiation systems are known as magnetic resonance (MRI), ultrasound (UG), camera-based systems and electromagnetic tracking [1-4].

One of the IGRT modes is kilovoltage cone-beam computed tomography (CBCT) or kilovoltage iterative CBCT (iCBCT). This imaging technique gives an essential information about patient positioning, and allows to improve geometrical accuracy of the target, and OARs localisation. Also, using kV-iCBCT gives an opportunity to follow different volume changes (bladder and rectum), which influences prostate movement as well. Due to this reason using kV-iCBCT images for the treatment planning is a *relevant* step improving planning target volume coverage, and reducing toxicity for the patients, because planning target volume margin could be minimized [5-6].

The aim of the master's final degree project is to plan treatment, using different imaging techniques (computed tomography and iterative cone-beam computed tomography) and compare, analysing dosimetry data changes of target volumes and organs at risk, for prostate cancer patients.

The tasks:

1. To evaluate volume changes of rectum and bladder for prostate cancer patients throughout the whole treatment period.
2. To analyse and compare the main dosimetry data of the planned treatment plans, using two different imaging techniques (computed tomography and iterative cone-beam computed tomography).
3. To evaluate iterative cone-beam computed tomography planning advantages, and disadvantages for the use in a daily clinical practice and provide possible recommendations.

1. Literature review

1.1. Cancer

Cancer is the most common health problem worldwide, often leading to death. According to World Health Organisation (WHO), cancer can be defined as a condition where cells begin to grow and multiply uncontrollably. As a result, cells of cancer can invade other parts of the body or organs, and damage them [7].

It is known that when tumour cells spread into other body parts that process is called – metastasizing. WHO states that 30-50 % cancer death could be avoided if the population takes preventive measures. These measures can reduce the certain chances of cancer:

- healthy eating habits: more fruits and vegetables
- avoid smoking and drinking alcohol
- get regular sports
- get regular health check-up
- recommended to get vaccine against human papillomavirus, and hepatitis B
- reduce exposure to sunlight, etc.

Another important thing is an effective, and productive response to diagnosed early-stage cancer. It means a higher probability of survival than death [7].

Number of different type cancer cases growth everyday. Cancer cases number for females was about 1,200000, while among males' it was around 1,500000 in European Union (EU) in 2020. The most common types of cancers among females are breast, colorectum, lung, corpus uteri, and melanoma; among males are prostate, lung, colorectum, bladder, and kidney (Fig. 1) [8-9].

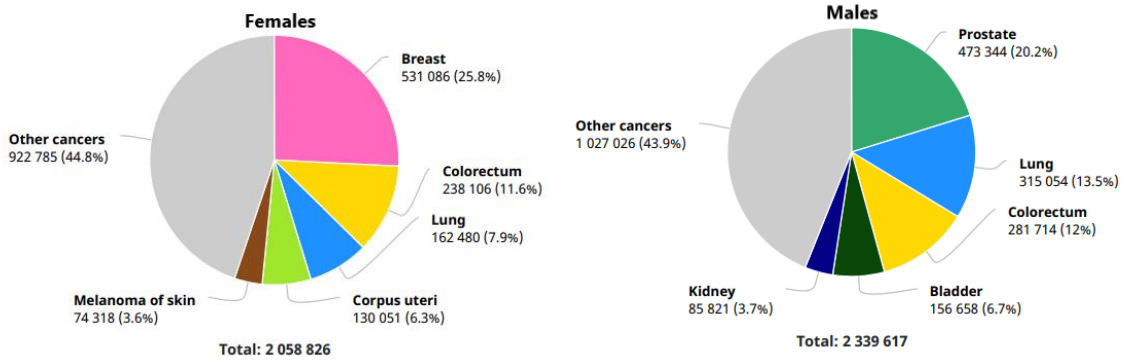


Fig. 1. Pie charts which represent a cancer type of prevalence among females and males in European Union in 2020 [8]

1.1.1. Prostate cancer

Prostate cancer is the most commonly diagnosed case among man, which contains ~20.2 % of all the cases (Fig. 2). Early-stage prostate cancer has no initial or severe symptoms while in late-stage may occur symptoms such as bone pain, failure of renal due to bilateral ureteral obstruction, fatigue etc. Prostate cancer diagnosis starts from prostate-specific antigen (PSA) analysis, and biopsies of prostate tissue by guided ultrasound. If prostate cancer is determined, it facilitates a certain treatment methodology. On the other hand, if disease has spread to the other organs, palliative treatment could be implemented, using a medication of pain, hormonal treatment, immunotherapy, chemotherapy, or

radiation therapy. Results of the treatment depends on patient age, tumour histology, and other health problems [19].

Prostate is a gland and one of the parts of the male reproductive system. Gland is pyramid shaped organ, which is located below the bladder, and in front of the rectum. Weight of the prostate is about 20 g. Prostate gland wraps the proximal urethra in lower pelvis. A capsule of fibrous encloses gland with all adjacent formations – vascular plexus, and nerves. Prostate apex is contacting penile urethra, and base of the prostate gland connecting to the bladder. The prostate gland has a different histological zone: central zone, transition zone, and peripheral zone (Fig. 2) [10].

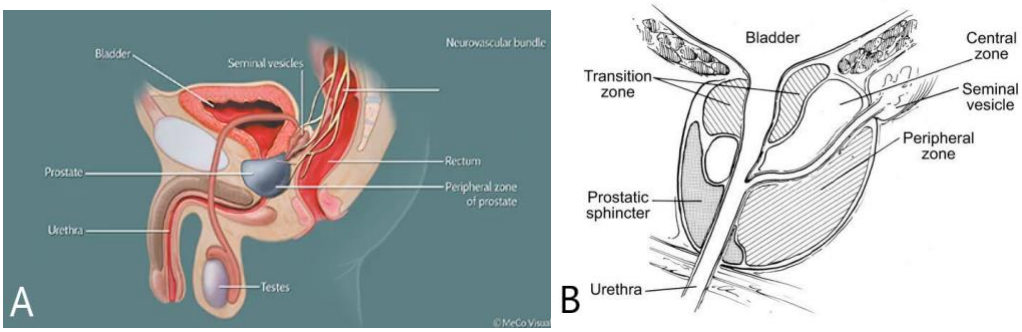


Fig. 2. A – Prostate gland anatomical location in body, B – Histological zones of prostate gland [10-11]

The prostate is the most commonly affected by these three clinical conditions: prostate cancer, prostatitis, and benign prostatic hyperplasia. M. Ittmann and etc. [12] observed that prostate cancer that occurs in the transition zone of the prostate has biological and clinical differences compared with cancer that occurs in the peripheral zone. The central zone of prostate is cone shape area, which base is wider. This anatomical site is not the place of origin of disease; however, this anatomical area can be impacted by secondary cancer [12].

It is known that adenocarcinoma is the most common type of prostate cancer. Prostate cancer occurrence could be related to family history, body mass index, ionizing or ultraviolet radiation, and smoking. Moreover, cancer of the prostate can spread through venous channels that connect to the lower lumbar vertebrae's venous channels [10].

1.2. Radiotherapy

Radiotherapy (RT) is one of the ways to treat cancer. An ionizing radiation is used to control locally and kill cells of cancer or reduce palliate symptoms of the patient. Depending on the type, localisation and spread of the cancer RT can be combined with surgery, chemotherapy, immunotherapy or with other cancer treatment modalities [13-15].

1.2.1. Types of the radiotherapy

Radiation therapy can be divided into two groups: internal and external (Fig. 3) [16].

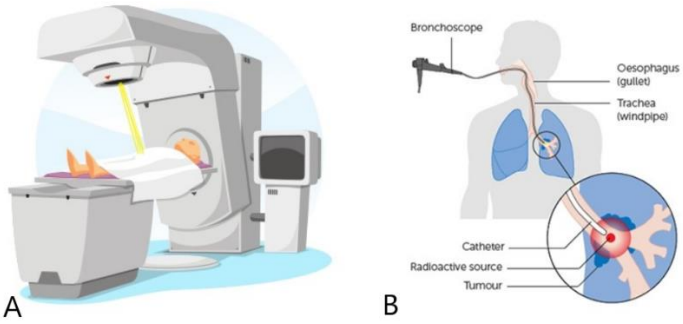


Fig. 3. A – External radiotherapy, when radioactive source is outside the body; B – Internal radiotherapy, when radioactive source is placed near or into the tumour [17]

Internal radiotherapy is a type of radiation treatment when the source of long-lived radionuclide is implanted into a tumour or surrounding tissue. It gives the opportunity to treat the smaller area with a higher total radiation dose in a shorter time in comparison external radiotherapy. Radionuclides are placed into a tumour by delivery devices like needles, applicators, or catheters using computed tomography (CT), and ultrasound (US). It helps to control the source position in the body. Radionuclides are sealed into forms such as pellets, seeds, or wires. Implants of the radioactive sources can be permanent or temporary. In internal radiotherapy are used radionuclides such as ^{137}Cs, ^{125}I, ^{103}Pb, ^{192}Ir, ^{198}Au, etc. The main types of internal radiotherapy are brachytherapy and radioactive liquid treatment (peptide receptor radionuclide therapy and radioimmunotherapy) [13, 16].

External radiotherapy is the treatment modality when the radiation source is outside the patient's body. High energy rays of ionising radiation reach the tumour located deep inside the patient. External beam radiation therapy procedures are performed in shielded rooms in hospitals by special machines of cobalt-60 or medical linear accelerators. The main types of external radiotherapy planning, and treatment techniques are conventional radiotherapy, stereotactic radiotherapy, conformal radiotherapy, image-guided radiotherapy (IGRT), intensity-modulated radiotherapy (IMRT), volumetric-modulation radiotherapy (VMAT) and therapy of particles [13-14, 16, 18].

1.3. Delineation of target volumes and organs at risk

In external radiotherapy one of the essential parts is to delineate the volume of the target. This is necessary for the precise dose to the tumour and, at the same time, protection of the surrounding tissues and critical organs as much as possible. Also, it gives an opportunity to make a high-quality dosimetric plan [19].

Target volumes consist of (Fig. 4):

- Gross tumour volume (GTV) is visible or felt by palpation. The radiation dose to GTV must be delivered to the whole volume to achieve maximum control of the tumour. GTV location, size and shape can be defined using an ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), and other methods [19-21].
- Clinical target volume (CTV) includes GTV volume and additional volume in which microscopic and subclinical extensions are likely to occur. Microscopic and subclinical extensions located in CTV should be sufficiently irradiated to achieve the goal of treatment [19, 22].
- Planning target volume (PTV) – according to IAEA publication Accuracy Requirements and Uncertainties in Radiotherapy is an additional margin added to CTV due to better geometrical ensures during treatment (deformations and mobility of organs, patient setup etc). The shape of the

PTV volume depends on technical planning and irradiation possibilities and conditions of a treatment. PTV volume takes into account margin which involves involuntary motion of organs, filling, and uncertainties of the dose administration [19, 22].

- Treated volume (TV) is an area of the tissues that are planned to receive the minimum dose determined by the appropriate radiation oncologist to achieve the treatment goal (eradication of the tumour) without exceeding possible complications. TV could differ from PTV, because it may be larger or smaller and with a simpler shape, it depends on the treatment method (IMRT, conventional/ conformal RT) [19, 22].
- Irradiated volume (IV) usually receives a dosage that is considerable in comparison to normal tissues tolerance. IV usually is determined by the treatment method [19].

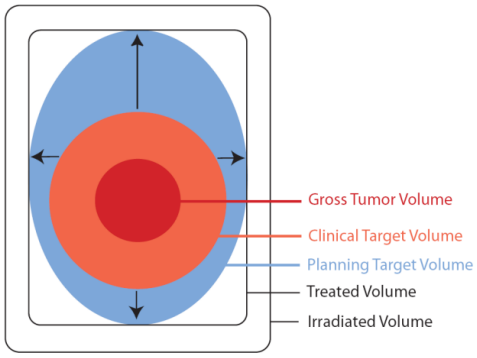


Fig. 4. Different volume illustration [23]

Organs at risk (OARs) are called critical structures, which have important functional properties and anatomically are located near the tumour volume. During radiotherapy, planning is needed to be considered for OARs, because irradiation could induce pathological changes and different side effects can occur. OARs can influence the clinical decision of the treatment, regarding the risk of toxicity on disease site, treatment method, previous treatment, patient age and other aspects. The dose received by the OARs is estimated using dose-volume histograms (DVH) (Fig. 5) [24-25].

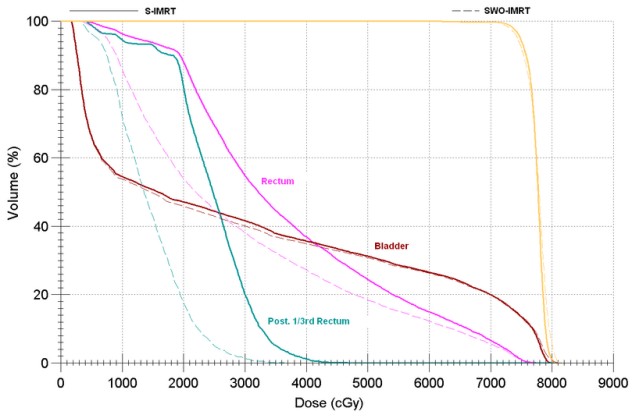


Fig. 5. Dose volume histogram for organ at risk and target evaluation [26]

According to American Association of Physicists in Medicine Task Group, 263 OARs are divided into recommended (tissues are contoured in all treatment cases) and considered (depending on treatment case, tissues may be required to contour). Recommended and considered organs for contouring when tumours of pelvis region are treated are presented in the Table 1 [25].

Table 1. Recommended and considered organs at risk [25]

Treated organ	Recommended	Considered
Bladder	- Bowel small - Colon sigmoid - Femur heads (L/R) - Rectum	- Bladder - Bone marrow - Bowel large - Prostate
Cervix/Uterus/Vagina/Vulva	- Bladder - Bowel small - Colon sigmoid - Femur heads (L/R) - Rectum	- Bone marrow - Bowel large - Kidneys (L/R) - Ovaries
Prostate	- Bladder - Femur heads (L/R) - Penile bulb - Rectum	- Bowel large - Bowel small - Colon sigmoid
Rectum	- Bladder - Bowel small - Femur heads (L/R)	- Bone marrow - Bowel large - Genitals - Vagina
Anus	- Bladder - Bowel small - Femur head (L/R) - Rectum	- Bone marrow - Bowel large - Genitals - Vagina

Movements of the prostate during radiotherapy treatment create some uncertainty related to the localization of the target and require additional intra-fraction shift margin. It is very important to take into account motion margins for the prostate gland. Additional margins to the target can be added using these techniques such as CBCT imaging before and after treatment procedure, EPID, and electromagnetic tracking systems [27].

Regarding Rassiah-Szegedi et al. [28] electromagnetic tracking during VMAT treatment procedure for the prostate intra-fraction motion could be successful. Obtained results showed that electromagnetic tracking gives better protection to the OARs compared to the conventional 5-7 mm margins, and recommended 3 mm margins for an interface of the prostate-rectum and 5 mm in other directions. Kupelian et al. [29] study showed that electromagnetic tracking used for intra-fraction motion of the prostate gland is dependent not only on a patient, but also varies between treatment fractions. Also, it is known that intra-fraction motion will be affected due to longer radiotherapy treatment. It was observed that 3 mm of internal margin could adequately represent 95 % of intra-fractional prostate motion up to 6 minutes during the treatment if additional measures are used such as fiducial markers, and an endorectal balloon. It means that real-time tracking can give an opportunity to reduce the PTV margin for 3-4 mm range, while without it – 5-8 mm [27].

1.3.1. Prostate contouring

Prostate gland gross tumour volume (GTV) can be determined by computer tomography (CT) and magnetic resonance imaging (MRI). It is known that prostate gland position may be influenced by bladder and rectum filling. It is recommended to keep the rectum and bladder the same filling before simulation of CT, and each radiotherapy fraction because it ensures accuracy of the irradiation dose to these organs, and the target [30].

Target volumes and OARs delineation for the prostate cancer patient usually is defined on CT simulation images. Target volumes are known as gross tumour volume (GTV), clinical target volume (CTV), and planning target volume (PTV). Organs which are nearby prostate such as bladder, colon, pelvis bone, rectum, femoral head, and others, are known as OARs, and can be contoured, if necessary. The target volume of the prostate must include the whole organ and its capsule, because prostate gland cancer usually starts with multifocal foci. For this reason, CTV is usually contoured without GTV. Invasion of the seminal vesicle probability becomes greater for intermediate or high-risk prostatic adenocarcinoma, and it is necessary to incorporate a seminal vesicle in CTV. If cancer has intermediate or low risk, the lymph nodes of the pelvis region are not added in CTV, but high-risk cancer of the prostate increases the probability of metastasis [30].

Prostate and seminal vesicles may be affected by bladder and rectum filling volume, the position of treatment, set-up errors, and breathing. Due to this reason, it is very important to determine precise margins of target volumes (GTV, CTV, PTV). Mainly movement of the prostate is in the superior-inferior and anterior-posterior directions, while smaller movements occur in the left-right direction. Usually is recommended to expand 5 mm CTV to PTV in posterior direction, and reduce irradiation of rectum. Irradiation of the pelvis lymph nodes due to prophylactic recommends 7-10 mm expansion into PTV, but if the imaging before irradiation procedure is used daily, margins can be reduced to 3-5 mm to the rectal direction (Fig. 6) [30].

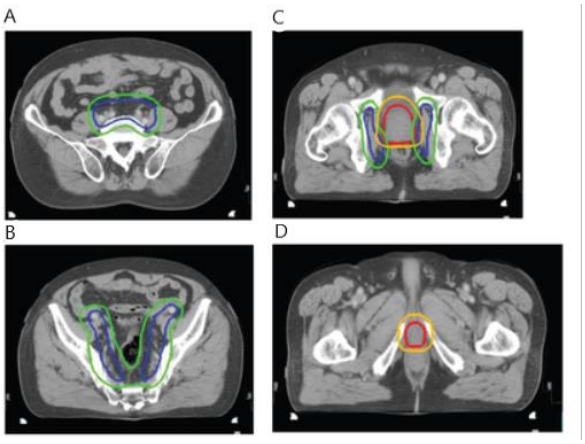


Fig. 6. Delineation of pelvis lymphatic drainage (PTV – green, CTV – dark blue), prostate and seminal vesicles (PTV – yellow, CTV – red) [30]

Target volume delineation of prostate also depends on the risk of cancer. It is known that prostate can be delineated for low-risk cancer, while prostate with seminal vesicles must be contoured with 1.0-1.5 cm in intermediate-risk cancer, and 1.5-2.0 cm must be contoured for high-risk cancer. Prostate contour in CT images must include entire prostate gland, its capsule and seminal vesicles. Lower boundaries have to cover apex of prostate for prevention of recurrence. Inferior boundary above penile bulb should be about 0.5 cm. The anterior border is the posterior margin of the pubic symphysis. The posterior border is adjacent to the anterior wall of the rectum, and the lateral border is adjacent to the medial edge of the obturator internus muscle. The area of the pelvis lymphatic drainage delineation is performed usually using Radiation Therapy Oncology Group (RTOG) recommendations [30].

Normal or healthy tissues and OARs contouring is also important as target volume contouring. OARs of the pelvis region are rectum, bladder, colon, heads of femur, pelvis bone, small intestine, kidney, and etc. Small and large bowels should include all intestinal wall into delineation. Whole bladder should be

contoured, while femoral heads include head and neck parts of the bone. Contouring of the organs are performed according to RTOG guidelines, as it was mentioned before [30].

The main difference from the target volumes is that OARs have a limitation of doses or so-called dose constraints. Doses must be reduced as much as possible, so minimizing a probability of the side effects. The main dose constraints for OARs, which are used for prostate cancer irradiation treatment planning are presented in the Table 2 [30].

Table 2. Dose constraints for the pelvis region organs at risk [30]

Organ	**Dose**
Bladder	V (≥50 Gy) <50 %, V (≥70 Gy) <30 %
Rectum	V (≥50 Gy) <50 %, V (≥70 Gy) <25 %, avoiding a dose "hot spot" on rectal wall
Femoral head and neck	V (≥50 Gy) <5 %
Small intestine	D_{max} ≤52 Gy, V (≥50 Gy) <5 %
Colon	D_{max} ≤55 Gy, V (≥50 Gy) <10 %
Pelvis bone	V (≥30 Gy) <30 %, mean dose <20 Gy

Seminal vesicles and prostate gland are the most common target structures, but they can also be avoided if cancer is not present. Prostate gland contouring necessitates a thorough understanding of prostate anatomy. Penile bulb contouring requires CT or MRI imaging with contrast in the urethra. It helps to contour it better because penile bulb has a great variability [31].

Pelvis organs recommendation of contouring is given in Table 3 [30].

Table 3. Contouring recommendations for pelvis organs [30]

Normal tissue	**Resources**
genitalia (men) genitalia (women)	Proposed genitalia contouring guidelines in anal cancer intensity-modulated radiotherapy
Anorectum, bladder, bowel bag, colon, femoral head, penile bulb, prostate, rectum, sigmoid colon, small bowel	Pelvis normal tissue contouring guidelines for radiation therapy: A Radiation Therapy Oncology Group consensus panel atlas.
Sacral plexus	Development of a Standardized Method for Contouring the Lumbosacral Plexus: A Preliminary Dosimetric Analysis of this Organ at Risk Among 15 Patients Treated with Intensity-Modulated Radiotherapy for Lower Gastrointestinal Cancer and the Incidence of Radiation-Induced Lumbosacral Plexopathy.

According to International Commission on Radiation Units and Measurements Report 83 (ICRU) [32], OARs are grouped into: serial, parallel, and serial-parallel (Fig. 7). This organ system is used to explain tolerance of OARs. Architecture of the organs has a strong relationship with a dose tolerance. Dose to the organs or tissues which are in "serial" group (e.g., spinal cord, optical nerve, optical chiasm), can not exceed the dose above the tolerance limits, because even small caused area can be impacted, and cause a complication, for example, myelitis. Irradiation dose to the organs which are in "parallel" group (lungs, kidneys) are limited by volume. Some organs have a combined architecture serial-parallel, for example, heart (serial organ – myocardium and parallel organ – coronary arteries) [23-24,33-34]. The main radiotherapy methods, their advantages and disadvantages are presented in the Table 4.

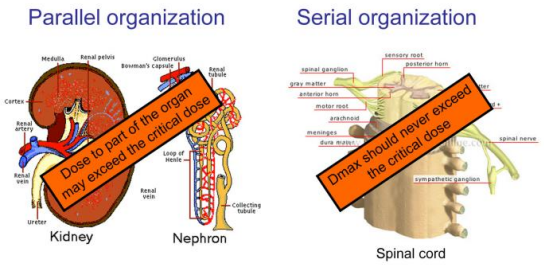


Fig. 7. Groups of OARs [34]

Table 4. Methods of radiotherapy, their advantages, and disadvantages

Treatment method	Advantages	Disadvantages
IMRT [16,35]	- 3D conformal radiotherapy - Less side effects - Precise dose into the target while sparing a normal tissues and organs - Rotation therapy (isocentric) - Multi leaf collimator	- High cost of implementation - Complex and time-consuming procedures - More sensitive to geometrical errors (immobilisation) - Need to be precise for target delineation
VMAT [36-37]	- Shorter treatment time (comparing with IMRT) - Linear accelerator rotates around the patient (360º) - Use arcs, that increase number of angles and reduce radiation dose to normal tissue or organs	- Requires specific quality assurance tests: beam flatness and symmetry measurements at used dose rate, MLC calibration, synchronization of the MLC, gantry, and dose rate
Stereotactic radiotherapy (GammaKnife, SBRT, CyberKnife) [16,36,38]	- No invasive - High doses delivered precise to the target - Use many different angles and reduce radiation dose to normal tissues - Sometimes enough only one fraction - Immobilisation helps to avoid geometrical error - Real-time tracking	- Increases the need for imaging – MRI - Need excellent management of motion and image guidance systems - Unclear about the problem for wound healing - There is no pathological confirmation
IGRT [36,39-40]	- Allow to change patient position and replanned radiation dose if needed - Increases accuracy of delivered dose to target and decrease dose to healthy tissues - Tumour control probability - Real-time tracking - Reduction of set-up error	- Additional low dose - Longer treatment time - Need special equipment (CBCT, US, electromagnetic tracking etc)
Conventional radiotherapy [36,41]	- Low cost of implementation - Most used for palliative treatment	- Not recommended to use for local control, survival, and toxicity to normal tissues
3D Conformal radiotherapy [36,42-43]	- Use CT scans to define organs and tissues in three-dimensions - Radiation beam shape are modified by MLC or Cerrobend blocks - Healthy tissues and organs receive small dose of radiation as possible	- Complicated planning of treatment - Need very precise countering of the target - Large volumes which get a low-intermediate dose (possibility of the secondary cancer

1.3.2. Movements of prostate during the irradiation procedure

Prostate is surrounding by seminal vesicle, lymph node, urethra, pubic bone but most important surrounding organs which are near prostate are bladder and rectum. Bladder and rectum are flexible organs, and due to the filling can change a volume. Moveable organs can not be fixed with any kind of bones, for this reason prostate location could be changed by bladder or rectum. Gurjar et al. [5] study showed that prostate gland may be displaced toward anterior direction of the patient due to the filling of rectum, while bladder with a different filling volume can displace the prostate gland toward the posterior direction. Therefore, bladder and rectum have high impact to prostate movements [44-45].

Motions of prostate can occur in all directions: superoinferior, anteroposterior, etc. (Fig. 8). Poli et al. [44] observed that during radiation treatment prostate movements can occur due to change in the volume of the rectum, for example, in the posterior and inferior orientations, the prostate could move up 13 mm and 8 mm, respectively. Other authors investigated prostate motion, and obtained results, which showed that anteroposterior and left-right directions margin value was equal 0.7 cm, and superoinferior direction – 1.1 cm. Some results of prostate movement showed that anteroposterior motion has a standard deviation of 1.5 mm to 4.1 mm, superoinferior motion has a standard deviation of 1.7 mm to 4.5 mm and lateral motion has a standard deviation of 0.7 mm to 1.9 mm. The study indicated that the movements were greater in superoinferior and anteroposterior direction. Accordingly, to the obtained results by different authors prove that the rectum filling is important factor for prostate motion occurrence, and an empty or full rectum causes different displacements of the prostate in the different directions [44-45].

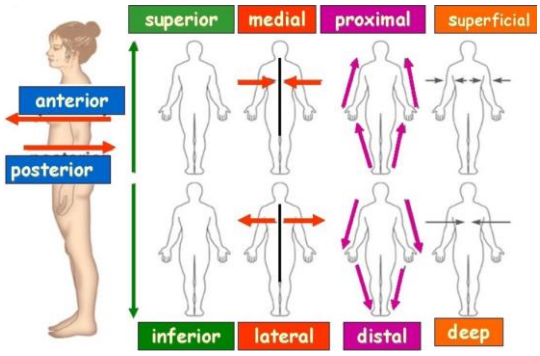


Fig. 8. Direction of organ movement [46]

Some movements can be divided into inter-fractional and intra-fractional shifts. The daily discrepancies between the position of the isocentre on the medical linear accelerator, and the defined isocentre of the irradiation plan are reflected by inter-fractional shifts, which represent movements between the separate fractions of irradiation (Fig. 9). The difference between the reference position of the patient or/ and tumour received by electronic portal imaging device (EPID) during image-guided radiotherapy are essential for the treatment procedure accuracy and optimisation. Inter-fractional movements occur due to patient geometric settings on the linear accelerator table, changes in target due to an altered increase or decrease in the patient's weight or tumour mass, and deviations for fixation aids for patient in daily settings. Therefore, shifts of inter-fractional movements could be reduced with online image-guided radiotherapy (IGRT) process [47].

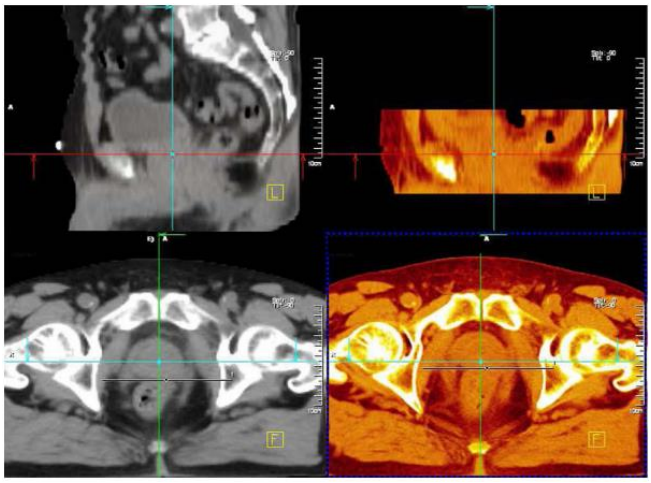


Fig. 9. Comparison between slice of pre-treatment (grey image) and planning slice of CT (colourful image) [48]

Intra-fractional shifts are known as movements, which occurs during a single fraction of the irradiation. It presents organs or bone structure changes or/and movements according to isocentre position with a position which was known previously before irradiation in a fraction of single treatment/ reference position (Fig. 10). Changes of motions are grouped into variations of external set-up, and motion of internal organs. The range of motion of a patient or organ within a segment can significantly affect the design of the protective margin during irradiation. For larger intra-fractional movements, larger protection margins should be used but for this reason it can create worse condition for organs at risk (OAR), and it can lead higher side effects of irradiation (due to radiation). Causes of the intra-fractional shifts divided into patient movements because of uncomfortable position during treatment procedure, and organ movements, for example prostate or lungs (breathing, rectum, or bladder daily filling) [47].

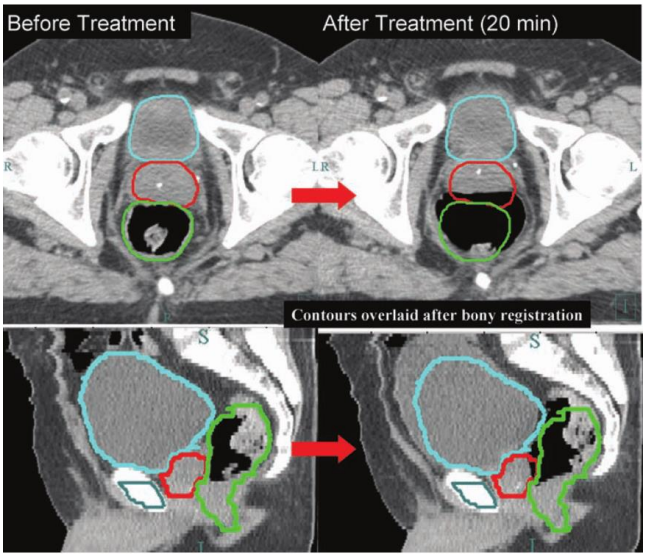


Fig. 10. Intra-fractional shifts of prostate after treatment. CT images were obtained before and after the IMRT treatment. Prostate (red contour) was shifted anteriorly for >5 mm. The other structures showed in a figure are: rectum (green contour) and bladder (blue contour) [49]

Movements of the prostate could be reduced partly by using immobilization devices: external or internal. External immobilization devices help to reduce positioning errors, while internal devices reduce prostate motion. One mostly used internal immobilization device for prostate motion reduction is endorectal balloon. Endorectal balloon is good as immobilization device and tool of localization. In research

Yartsev et al. [27] were used an endorectal balloon, and it was associated with margins of PTV about 3-5 mm, to be able adjust intra-fraction movements of the prostate.

Bladder is another moveable organ which due to volume changes could influence position of the prostate gland. Mullaney et al. [50] and Fujioka et al. [51] studies showed that is possible to ensure consistency of the bladder volume before each treatment fraction and adopt different protocols of standardised hydration. Pang et al. [52] in they study used an empty bladder protocol, based on the fact that constant volume of bladder in the treatment of prostate cancer could provid stability of the target volume. Later, hydration protocol of the full bladder was adopted according to cone beam computed tomography (CBCT) availability, and this protocol gave an opportunity to displace a small bowel from field of treatment, it is especially important when pelvis nodal are irradiated. It was observed that a full bladder can reduce setup errors of the inter-fraction shifts, but it is important to mention that to maintain a constant bladder volume is a real challenge. If a special hydration protocol is applied to patient treatment of prostate cancer, usually the patient gets information about hydration protocol (before treatment procedure patient has to empty a bladder and when to drink a 400-600 ml of water). Pang et al. [52] found that volume of the planned bladder greater than 200 cm^3 is related to a decreasing mean value of the intra-fraction motion of prostate in anterior/posterior and superior/inferior directions.

1.4. Different techniques of real-time monitoring: IGRT

During radiotherapy is very important to ensure precise dose delivery to the tumour and ensure safety to normal tissues and organs as much as possible. Over radiotherapy treatment period internal anatomy changes occurs (tumour shrinkage or progression, weight loss, and etc.), which are called intra-fraction motion (mentioned in a section 1.3.2. “Movements of prostate during the irradiation procedure”, and these motions could be successfully checked using the image-guided radiotherapy (IGRT). Anatomical changes occur due to the drift of target, bladder or rectum filling, peristalsis, while faster motion occurs due to breathing or cardiac activity. Therefore, radiotherapy treatment due to anatomical changes could have some sort of dosimetric effects. Consequently, real-time monitoring methods give an opportunity to follow anatomical changes and make a certain adjustment [53].

IGRT corrections could be made online or offline. When adjustments are made offline, images are obtained before radiotherapy treatment and later (after irradiation procedure) matched to the standard/ reference image. The idea of this strategy is to find out a systematic setup error and try to reduce it as much as possible. Based on a setup data obtained by a combining information from the different patients treated with the same protocol, the standard error of the population at the treatment facility can be found. Offline adjustments include so called “No action level” and “Shrinking action level” protocols. Margins of the PTV depend on individual and systematic errors determination [1].

Online IGRT correction consists of image acquisition and their verification and adjustment if it is needed before each fraction of the treatment procedure. The goal of online IGRT strategy is reduction of systematic and random errors. Site of the treatment and error magnitude may define frequency of online imaging. Anatomical sites such as pelvis, abdomen area may have large daily motion or anatomical areas where even a tiny motion may change distribution of dose for critical structures, due to this reason it is the best to control it with a daily imaging procedure. Goyal et al. [1] experience showed that the highest errors could occur for thorax, abdomen, and pelvis regions, while the smallest one – for head and neck cancer irradiation.

1.5. Non radiation based IGRT techniques

It is known that IGRT imaging techniques can be divided into two groups: ionising radiation-based and non-radiation-based. Non-ionising radiation-based systems include ultrasound-based systems, electromagnetic tracking system, MRI-based systema, and camera-based system [1].

1.5.1. Camera-based monitoring system

Camera-based monitoring method is used for the patient's positioning, and intra-fraction motion monitoring. The system provides an opportunity to identify reference setup point position of the patient and compare it with a reference point location in coordinate system. It helps to reconcile isocentre of treatment couch with plan isocentre. One tool of the camera-based system is *AlignRT*. System tracks the surface of skin and gives response in real-time. Camera-based systems are applicable for breast and prostate cancer treatment, geometric accuracy is about 1 mm or 2 mm [1-2].

Camera-based monitoring system consist of a pair of infrared cameras, custom-made control system, and tracking tool: infrared markers (Fig. 11). Infrared-based monitoring system has two cameras, mounted on the floor. Reflective markers are placed on patient surface. Sensors of infrared cameras are connected with control software, installed in the treatment, and control rooms for a better interaction [54].

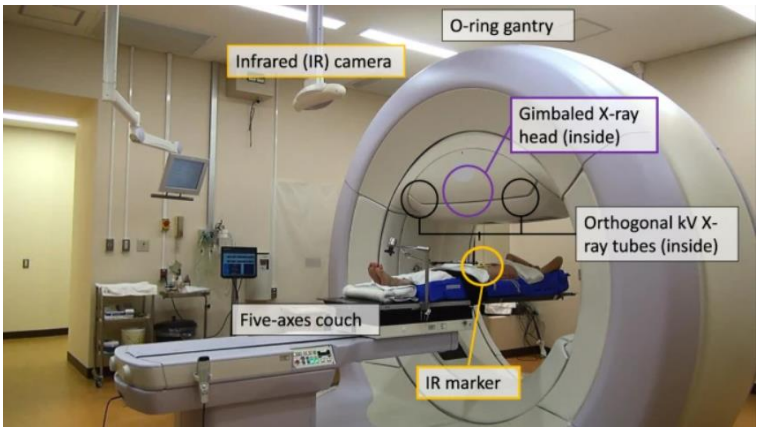


Fig. 11. Camera-based (infrared) monitoring method [55]

1.5.2. Electromagnetic Tracking systems

One of the electromagnetic systems used in radiotherapy for a real-time tracking is *Calypso* (*Varian* Medical Systems). Performing real-time tracking by this method, three transponders (beacons) are implanted in to treated organ, electromagnetic (EM) source, and receiver are placed above the patient during radiotherapy treatment. Beacons are invasively placed within the tumour (Fig. 12). EM receiver detects transponder location, which responds to EM signals sent by the array. *Calypso* system is used for intra-fraction motion tracking [1].

Another electromagnetic system is *RayPilot* (*Micropos* Medical AB). System composed of wired transmitter, detector array, and software. Wired transmitter is implanted into the treated organ, and after radiotherapy treatment course is removed. Software of electromagnetic system is needed for evaluation of transmitter position, and detector array (receiver plate). Signal of transmitter is detected by detector array, which is calibrated to the machine isocentre, and the EM system can locate the correct position of isocentre relative to the observed transmitter position using transmitter coordinates (coil centre point), and treatment isocentre in the planning CT [56].

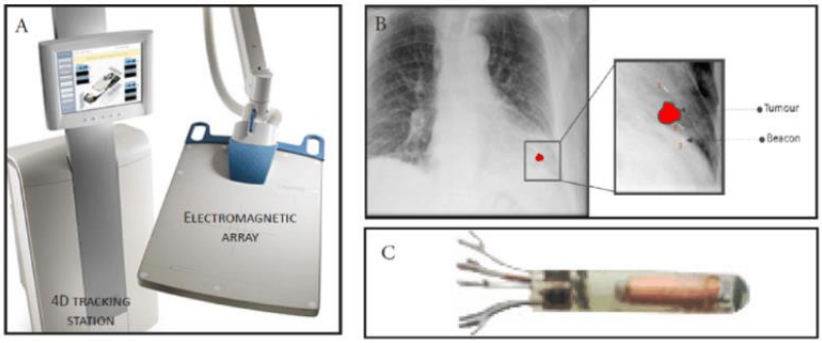


Fig. 12. A) *Calypso* tracking system B) Fluoroscopic image of implanted beacon in tumour C) Beacon [57]

1.5.3. Ultrasound-based systems

3D ultrasound (US) imaging is used for daily a tumour localization and verification before radiation treatment delivery. US imaging are mainly used for breast, gynaecological, and prostate verification. This method of imaging allows to perform a daily visualisation of prostate and compare with a reference US or CT image. In this case, daily prostate visualisation is important for the prostate moving due to rectal and bladder filling. Systems of ultrasound allow to get images in real-time with a good contrast of soft tissues, without ionising radiation. Internal tissue or organ deformation and motion are detected directly at high spatial, and temporal resolutions. US imaging require special skills to get high quality images, which could be compared with the other used IGRT techniques [58-59].

One part of the US imaging system is the probe with piezoelectric elements which creates high-frequency sounds waves and transmit it into the body (Fig. 13). Propagating waves encounter with different tissues and organs. Between propagating wave, and tissues are different acoustic impedance, for this reason part of US waves are reflected, and other part of waves keep penetrating deeper into the body. Reflected waves are received by transducer, and all information are processed to produce an image [59].

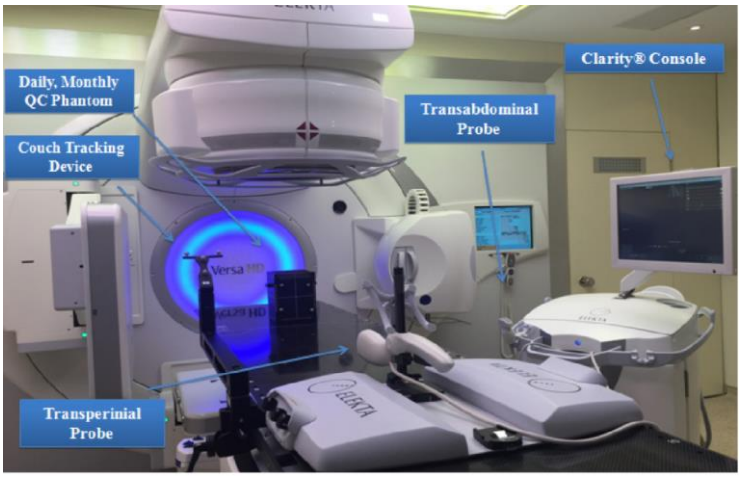


Fig. 13. Ultrasound system *Clarity*® [60]

There are US probes with various shapes and characteristics for different procedure type. During radiotherapy for prostate and OARs imaging is used three techniques of US imaging: transrectal, transabdominal, and transperineally [59].

Usually for US imaging are used these systems: *SonArray, Clarity or BAT. Clarity*^{TM} *(Elekta)* US system is designed for intra-fraction shift monitoring. System has 3D transperineally US transducer which is

approved special for prostate imaging, and transducer easy to adapt with standard linear accelerator (C-arm). Autoscan is integrated in US system and provides flexible system of monitoring that is not affected by metal implant *Autoscan* integration with linacs of *Elekta* allows to make movements softer using automated couch gating or correction [59].

1.5.4. Magnetic resonance-guided imaging

Linear accelerators could have integrated magnetic resonance imaging (MRI), and it is called MRI guided IGRT (Fig. 14). MRI-guided imaging provides highest quality contrast of soft tissues, improve visualisation of the organ motion, and has a greater capacity for imaging tumour, and tissue physiologic structure, in comparison to CT. Therefore, it is known that patient with pacemakers and other metallic implants or sizeable patient can not be examined using MRI. MRI system strengths of magnetic fields can be from 0.35 T to 1.5 T. MRI has online and offline platforms where treatment planning adjustments can be done [1,53,61].

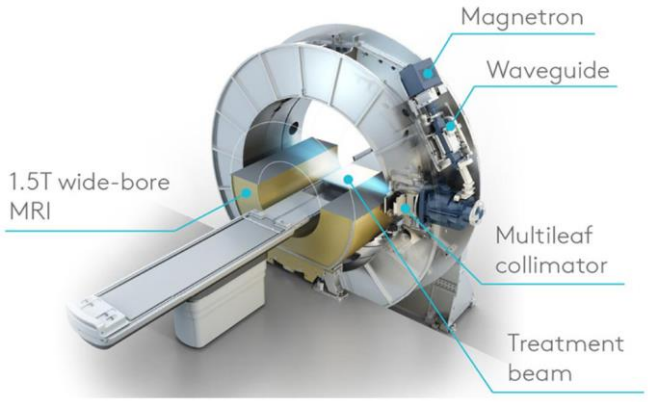


Fig. 14. MRI-guided *Elekta Unity* system [62]

Online MRI-guided radiotherapy is useful for intra-fractional and inter-fractional adjustment to organ movements. Treatment planning adjustments could be done in real-time before each fraction over radiotherapy treatment because targets can be affected by sporadic motion, like prostate or rectum tumours or continuous motion, such as lung or liver tumours. Good soft tissue contrast allows to contour target without contrast media. MRI-guided system improves visualisation of OARs and helps to reduce margins of uncertainties [61].

Offline MRI simulation takes an important role in treatment planning. Offline simulation adds immobilisation devices which will be used during radiotherapy treatment and simulate accurate position of patient as possible. However, immobilisation device due to a higher distance between the patient and receiver coil can loss signal-to-noise ratio. To improve the signal-to-noise ratio, it is possible to construct a flexible receiver coil that may be out between immobilisation device and patient. In comparison with CT, MRI gives better intraprostatic anatomy visualisation, and better contouring of the glandular prostate tissue. MRI gives access to data about physiologic characteristic (perfusion, diffusion), and makes additional instructions for the target definition. Physiologic information can provide painting of dose, and show part of tumour which is the most radioresistant. The latest improvement of offline MRI system uses an artificial intelligence for automatic identification of structure and segmentation in plan of treatment [61].

Currently, there are available the *ViewRay MRIdian* and *Elekta Unity* systems of MRI-guided radiotherapy.

1.6. Ionising radiation based IGRT systems

Ionising radiation-based systems includes MV electronic portal imaging device (EPID), kV on-board (OBI), cone-beam computed tomography (CBCT), tomotherapy (MeV helical CT), and in-room helical computed tomography. Imaging systems use keV or MeV energy and provides 2-dimensional (2D) or 3-dimensional (3D) images [2].

1.6.1. Electronic portal imaging device

Electronic portal imaging device (EPID) is used for verification of patient setup during radiotherapy treatment. EPID allows to get a high quality 2D portal image, and evaluate patient treatment in real-time (Fig. 15). It may be for daily imaging or some other schedules/ frequency, it depends on treatment localization. Different systems for imaging can use keV or MeV x-rays. Images obtained with keV x-ray energy usually have a better contrast, while images obtained with MeV energy present less distortion, and it is better for the patient who have, for example, metallic implant (hip prothesis, dental, and etc.) [1,63].

EPID system have online and offline correction protocols. Middleton et al. [64] research results showed that online protocol has a significant reduction in a random and systematic errors. This method allows easy identification systematic and random variations and makes a possible correction for treatment plan. It is known that offline correction protocols, allows to reduce systematic errors, but has lower correction effect on random errors. Also, offline protocol does not allow to estimate the tumour in a real-time [64].

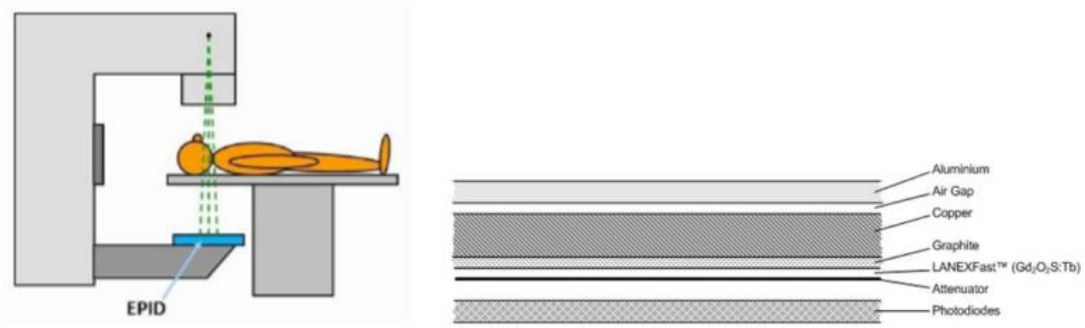


Fig. 15. EPID system and components of a EPID system plate [65-66]

1.6.2. Helical tomotherapy

Helical tomotherapy (HT) is an image-guided radiotherapy method which combine linear accelerator with 6 MeV energy and helical CT scanner with 3.5 MeV energy (Fig. 16). Usually, HT is a type of intensity-modulated radiation therapy (IMRT). Images of daily verification are received when ring gantry continuously rotates, and couch are moving into the gantry at a constant speed. Linear accelerator and system of detector array are installed opposite to each other. During treatment, radiation dose to the patient is collimated by multi-leaf collimator (MLC), while during daily verification all MLC leaves are opened [67-69].

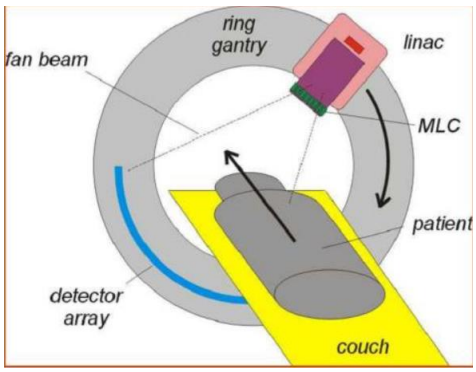


Fig. 16. Scheme of helical tomotherapy [69]

1.6.3. Computed tomography on rails

Computed tomography on rails is a system installed in radiation treatment room (Fig. 17). Linear accelerator and CT are connected through a rail system. CT-on-rails difference from diagnostic CT is larger size of bore, diameter is more than 80 cm. It is for immobilisation devices which may be used during radiation treatment procedure [1, 70].

Advantages of CT-on-rails are higher quality of images, more acceptable for contouring than CBCT images, also CT-on-rails can use lower dose protocols. One possible disadvantage is possible setup errors when treatment couch changes its position [67, 71].

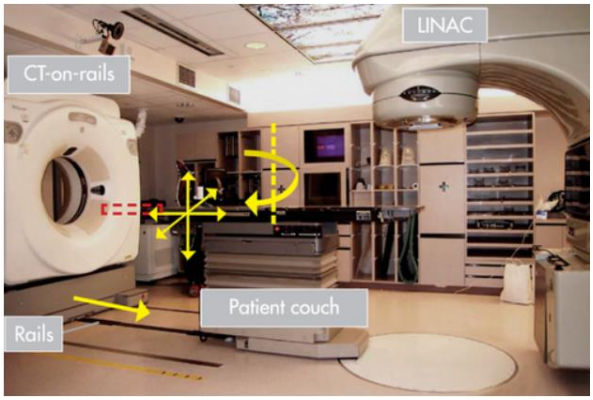


Fig. 17. Computed tomography on rails and Linear accelerator system [72]

1.6.4. Cone beam computed tomography

Cone beam computed tomography (CBCT) becomes an important part of radiotherapy for image guidance (Fig. 18). CBCT gives good detectability of soft tissues for accurate localization of the target. Images obtained by CBCT are 3D. New improvement in CBCT technology gives an opportunity to get images during treatment, images also can correlate with breathing, also quality becomes greater, and patients' dose is increasingly reduced. This method is constantly evolving and changes 2D and MV imaging of IGRT [73-74].

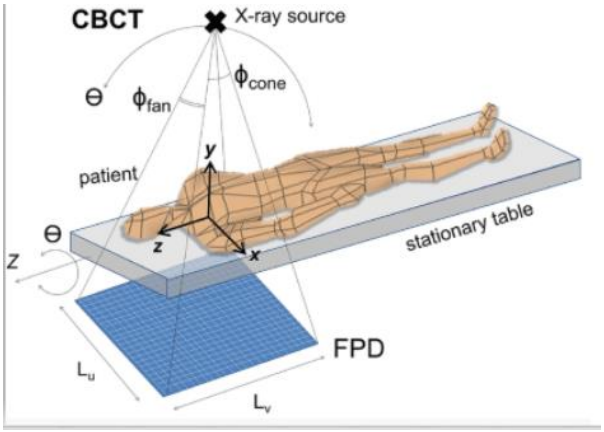


Fig. 18. Scheme of CBCT operating principle [75]

CBCT is essential procedure to follow inter-fractional and intra-fractional motions in target area. Daily imaging procedure may improve localization of immobilisation devices and fiducial markers. Also, CBCT takes important role in margin reduction for anatomical sites such as prostate, head and neck, lung. One of the examples could be lung stereotactic radiotherapy, CBCT improves detection of inter-fractional and intra-fractional motion and reduces margins of the treatment (area). Compared with CT, CBCT have many advantages: low dose of radiation, scanning speed, high spatial resolution, and convenient adjustment of the treatment plan [74].

Other advantage of the CBCT is adaptation of the treatment. During treatment period patient may lose weight or may tumour shrinkage due to head and neck cancer, or could occur deformation of the target, this is seen in prostate cancer. Also, can occur motion shifts due to breathing in lung or pancreas cancers. For this reason, CBCT lets to evaluate the reatment plan in 3D images and made an adjustment if required over the treatment course [74].

CBCT corrections have two strategies: online and offline. Online corrections are done immediately after image acquisition. Images are analysed and the necessary adjustments are applied before each radiotherapy procedure. This correction strategy removes random and systematic errors effectively. One disadvantage of this correction method is that analysis and corrections of images must be done quickly, and unambiguous because it increases treatment time and dose of radiation.

Offline correction images are analysed and adjusted later/ after irradiation procedure. Offline correction protocols have two possible methods: *Shrinking action level* (SAL) and *No action level* (NAL). Usually, are used NAL method for corrections. Systematic error which is determined as the average of the mistakes found in the first n fractions, is corrected systematically in a following session, with no tolerance limitations. Also, could be done extended NAL procedure for weekly checks. If the error is less than tolerance margin, no further corrections are required, but if error is higher than tolerance margin, need to be obtained more images to identify the error, and in this situation are used SAL protocol to make a correction [67].

CBCT have two different energies: megaelectronvoltage (MeV) and kiloelectronvoltage (keV) (Fig. 19), because it uses 2D collimated rectangular beam or beam of cone shape, and flat panel detector (FPD).

One of the IGRT category is MV-CBCT. During MV-CBCT imaging is used treatment beam and flat panel detector in an opposite side. Although CBCT uses a sub-optimal energy for imaging, MV-CBCT

imaging uses less equipment and provides better images of patients who have, for example, metal implants.

Another category of IGRT – kV-CBCT. System use keV x-ray energy and a flat panel detector which is positioned perpendicular to the beam of treatment. In comparison with MV-CBCT, kV-CBCT gives lower doses to the patients, and images are a much higher quality [57]. kV-CBCT are mounted on the gantry (Fig. 17). It is possible to obtain not only planar images, but also to get multiple projections with 360-degree rotation, and it is called a *cone beam computed tomography scan*. Images present 3D information of bone and soft tissues in sagittal, transversal, and coronal slices [67].

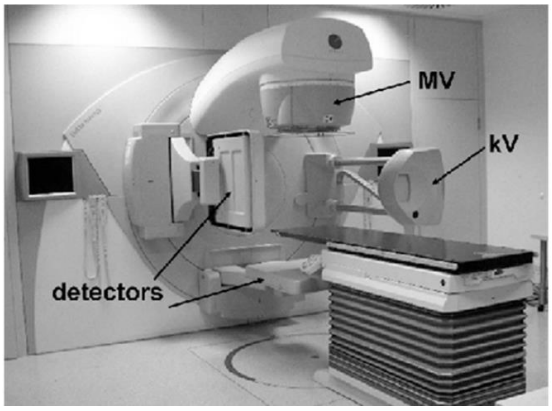


Fig. 19. *Elekta Synergy* linear accelerator with integrated cone beam computed tomography [76]

A summarized information about all real-time tracking systems is presented in the Table 5 .

Table 5. Real-time monitoring systems

Real-time monitoring method	Internal/ External	Dimension	Additional radiation	Additional equipment to linear accelerator	Geometric accuracy, mm	Average dose per image/scan, mGy
Camera-based (infrared – *AlignRT*) [1, 53]	External	6DoF surface*	No	Yes	1-2**	-
Electromagnetic tracking (*Calypso*) [1, 53]	Internal	3D	No	Yes	<2	-
Ultrasound-based (*SonArray, Clarity or BAT*) [1, 53]	Internal	3D	No	Yes	3-5	-
MR-guided imaging (*ViewRay MRIdian, Elekta Unity systems* [1, 53]	Internal	2D cine	No	Dedicated device	1-2	-
EPID [1-2, 53, 77]	Internal	2D	Yes	No	1-2	1-3
Helical tomotherapy [1, 53, 77-78]	Internal	3D	Yes	Dedicated device	≤1	10-30
CT on rails [1,77]	Internal	3D	Yes	Dedicated device	≤1	10-50
CBCT [1, 53, 77]	Internal	3D	Yes	No	≤1	30-50

*6DoF – six degrees of freedom.

**only useful in cases where an exterior surface can be used as a reasonable surrogate for internal motion or position.

1.7. Radiotherapy treatment planning

Radiotherapy treatment planning begins with scanning the patient with CT. Scanning protocols are chosen by anatomy area of the patient. Images of CT allow identified geometry and position of the tumour, and normal tissues. Also, CT images provide electron density information about organs and tissues, which are near the tumour, this information is important for dose calculation. 3D images give opportunity to create high-quality radiotherapy treatment plans [79-80].

For radiation therapy treatment planning not only CT scanning can be used. Other options can be magnetic resonance imaging (MRI) and positron emission tomography (PET). MRI and PET are imaging options which gives additional information about tumour geometry, and localisation for better radiation therapy treatment planning [81].

MRI provides better visualisation of soft tissues and their boundaries comparing with CT imaging. Other of many MRI advantages is non-ionizing radiation during procedure, this imaging method use waves of radiofrequency to generate the signal. On the other hand, MRI have some disadvantages due to artifacts of the image, and deficiency of information about tissue density. In the prostate tumour, radiation therapy planning MRI is used for prostate outlining. Good visualisation of soft tissues helps to contour the prostate, rectum, and bladder [81-82].

Other planning method is PET. Principle of PET is based on radiolabelled compound distribution in the human body. Scanning images of the PET shows most metabolically active organs or tissues. The radiotherapy treatment plan is based on the spatial location of the radioactive compound. Sometimes for the better results of MRI and PET can be combined together (Fig. 20) or with CT imaging. PET/MRI combination allow to visualize tumour and tissues volumes very accurately, anatomy and functionality, this is important, and for prostate tumour [81,83].

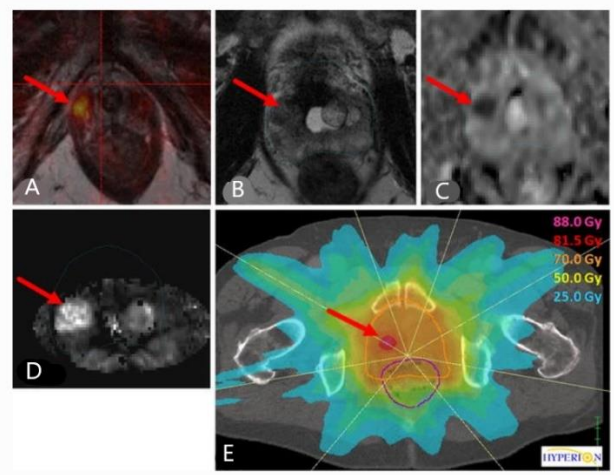


Fig. 20. PET and MRI combination. A) T2-weighted sequence MRI B) and C) MRI imaging D) dose painting E) dose distribution on different volumes of the tumour area [83]

However, CT is more commonly used than PET or MRI for fast scanning, easy dose calculations, and 3D images.

Radiation treatment planning includes two parts, it is a planning of technical treatment and clinical treatment. Technical treatment planning is responsible for these parts: patient positioning, radiation beam placement, and additional aperture shapes which help to achieve dose distribution to the volumes of the target and protect critical organs. While clinical treatment planning includes the intent of the

treatment, prescribed dose, and treatment method. The most important things in the treatment plan are beam numbers and energies, beam orientations and shapes [84].

Radiotherapy treatment plans can be varied from simple to complex and include many types: 2D, 3D, VMAT, IMRT etc. Today usually are used 3D plans which a created-on CT images after CT simulation [84].

VMAT radiotherapy plans has one or more arcs. Arcs does not include entire PTV, and can ensure protection of the OARs, but still provide designated dose coverage to the PTV. While IMRT radiotherapy plans, which are used, and for prostate cancer treatment, used fixed-angle beams (from 7 to 9 beams). Beam intensities varied and are measured by MU [84].

Initial plan of the radiotherapy treatment consists of prescribed dose which is emitted to the primary tumour, lymph nodes and other targets through a number of fractions. The lymph nodes and other targets gets lower dose than primary tumour. At times, an additional radiation dose may be given to the patient, and it is called simultaneously integrated boost (SIB) dose. This additional radiation dose is delivered to primary tumour to ensure a lower chance of the tumour recovering [84].

1.7.1. iCBCT planning

Imaging of the CBCT takes important role in the adaptive radiotherapy (ART) treatment due to real time tracking of anatomical changes, treatment plan adaptation, precise dose to the tumour, and can be used for organs contouring. The CBCT imaging has attracted a great deal of interest because it can change the standard planning of CT or can be used instead CT planning [85].

Company *Varian* has started developing a new algorithm of reconstructions, which is called *AcurosXB iCBCT* algorithm. Standard CBCT images reconstructed by *AcurosXB iCBCT* algorithm becomes iCBCT images. If iCBCT image has smaller FOV, the additional images of CT are stitched to compensate FOV. These generated images are called extended iCBCT images [86].

HU et al. [85] state that this algorithm reduces artefacts, improves HU values, and quality of the image. Better quality of iCBCT image ensures better soft delineation, that is important for contouring process. The primary plan of the radiation treatment was copied on CBCT for dose calculations, and after was reconstructed by algorithm to get iCBCT images. Author results showed that iCBCT reconstruction protocol is suitable to use to for dose calculations and varied ±2 %. Other author Jarema et al. [87] after research results confirm that dose calculations based on iCBCT images of pelvis is accurate, and radiotherapy planning can be planned on these images. In the Figure 21, are given all image types.

Also, in ART CBCT has advantages for efficiency of the time, cost, and much lower doses of radiation comparing with CT which can be used for re-scanning.

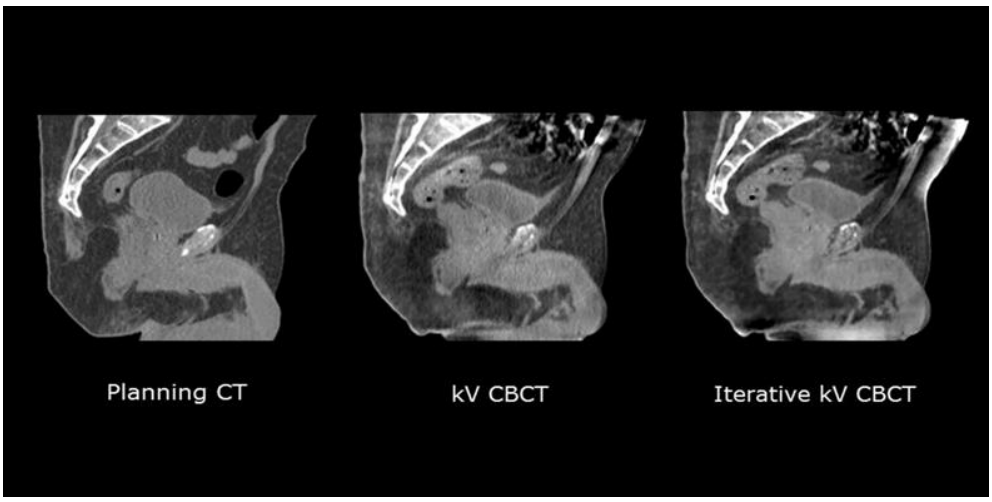


Fig. 21. Sagittal images of pelvis area (CT, kV CBCT and iCBCT

1.8. Summary of literature review

The prostate cancer can be treated by two radiotherapy methods: external and internal. In external radiotherapy is very important to delineate target volumes for precise dose to the tumour, and protection of the normal tissues. The contouring process is helpful, identifying contour of target and critical organs. The bladder and rectum are organs which change a volume during the treatment period. In this way, to follow how volumes have been changed are used one of the IGRT methods, for example, CBCT. IGRT is classified into two groups: based on ionising radiation and based on non-ionising radiation. These imaging techniques are important to be used for patient dose delivery evaluation, tumour and OARs localization, treatment plan verification. CBCT systems has two different energy ranges: megaelectronvoltage and kiloelectronvoltage. kV-CBCT is much better for different tissues and tumour visualization than MV-CBCT. Radiotherapy treatment planning begin from CT simulation, and on the CT images treatment plan is created. Before each radiotherapy fraction CBCT imaging is done. CBCT images can be reconstructed by iterative algorithm for iCBCT images, which are used for anatomical changes tracking and for radiotherapy plan adaptation.

2. Materials and methods

Cone-beam computed tomography (CBCT) takes an important role in radiation therapy and is one of the IGRT methods used for visualization. It allows to reduce volume of tumour (PTV), and to ensure a better protection of OARs throughout the treatment period Moreover, it improves precision of the dose delivery to the target and increase opportunity to reduce toxicity for the patient. Also, it is important for verification and correction of the patient position before radiotherapy procedure. This periodic image guidance before each fraction helps to eliminate uncertainties related with treatment in real time. Especially, in pelvis area where can occur large daily shifts. In other words, process of IGRT ensure that the delivered treatment matches with planned treatment and minimizes uncertainties. The other possibility to use CBCT imaging technique is treatment planning, using so called iterative CBCT (iCBCT) images [1].

This research was performed in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Oncology Hospital in the Radiotherapy department.

2.1. Linear accelerator *Halcyon v3.1*

Halcyon v3.1 is a new linear accelerator, which was installed in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Oncology Hospital, Radiation Therapy department in 2021 (Fig. 20). Halcyon is made by Varian company (Varian Medical Systems, Palo Alto, CA, USA), and mainly is used for radiotheraphy treatments such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) [88].

Fig. 22. Linear accelerator *Halcyon v3.1*

Linear accelerator *Halcyon* is a delivery system which is based on a ring principle (Fig. 21). It contains a flattening filter free (FFF), which produces a photon beam with 6 MeV energy. This beam is used for imaging and for radiotherapy treatment. Delivering of the beam is fast, linac ring velocity is 4 RPM with a maximum dose rate 800 MU/s. Field of view (FOV) of linear accelerator is (28 x 28) cm^2, but due to a dual isocenter the maximum length of the treatment field can be equal to 36 cm. Multi-leaf collimator (MLC) and the arrangement of the leaflets is such that each leaflet is offset by 5 mm from each other, it helps to reach efficacious shaping at isocenter (Fig. 22). MLC consists of 28 leaves with 1 cm width, and are projected at isocenter, maximum velocity of the leaf is 5 cm/s [88-91].

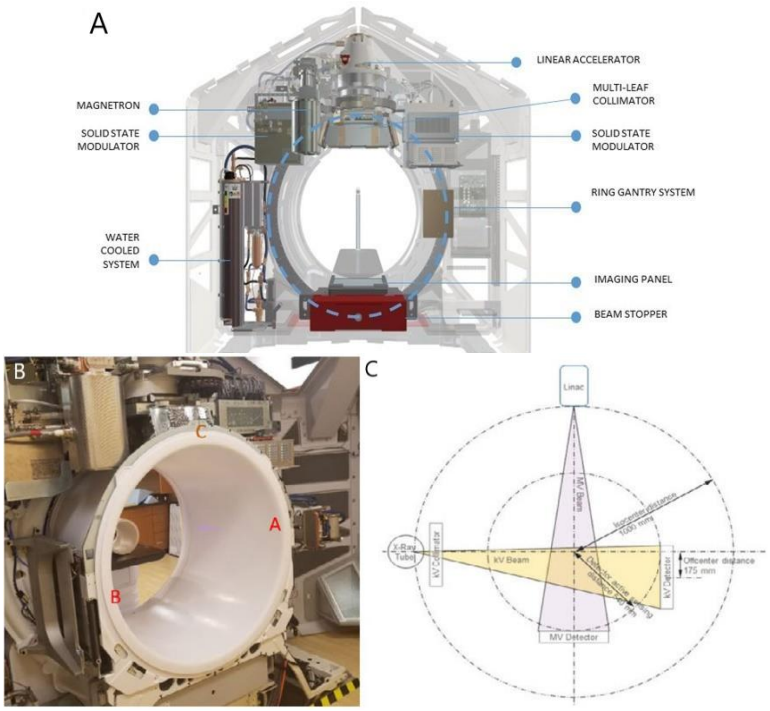


Fig. 23. A) Schematic view of *Halcyon* photon beam delivery system; B) Image of mounted kV source (A), detector of kV (B) and beamline of MV (C); C) Representation of kV and MV imaging systems [91-92]

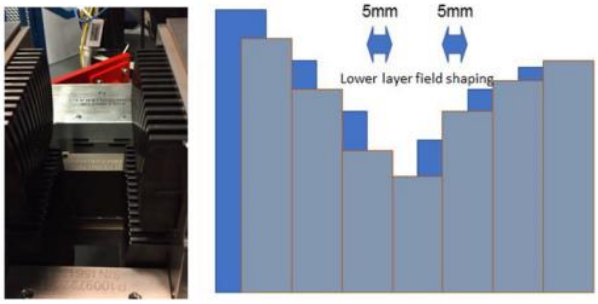


Fig. 24. Dual-layer MLC. Different blue tones represent a 5 mm shaping of field [91]

Patient is aligned by internal lasers to isocenter, moved into the bore to start a treatment procedure [90].

The most important feature of *Halcyon* is cone-beam computed tomography, it is one of the image-guided radiotherapy (IGRT) method. The linear accelerator *Halcyon* has an integrated a kilovoltage (kV) and megavoltage (MV) CBCT imaging systems. In this research was used a kV-iCBCT imaging technique for re-contouring OARs and treatment planning.

2.1.1. Cone-beam computed tomography and computed tomography imaging techniques

The main characteristics of the linear accelerator *Halcyon* kV-CBCT imaging system are presented in the Table 6.

Table 6. Linear accelerator *Halcyon* kV imaging characteristic [88]

Modes	11 protocols
Potential	80-140 kVp
Scan time	from 16.6 s (Head, Breast, Thorax modes) to 40.6 (Pelvis large mode)
Scan range	24.5 cm
Scan diameter	49.1 cm
Imager	17.5 cm lateral offset
Bow-tie	Half bow-tie/titanium filter
Pixel resolution	1280 x 1280 (43 x 43 cm panel)
Reconstruction	2 mm slice thickness
Reconstruction algorithm	Conventional FDK (CBCT), iterative process (iCBCT; nonlinear/statistical)

kV-CBCT has eleven scanning protocols. Scanning energies can depend on a protocol and varies from 80 keV to 140 keV. These energy settings can not be changed [88]. Only mAs parameters and longitudinal scanning range can be changeable. Acquisition of images are performed in full 360^{o}, and makes a different projection number. Size of field of view (FOV) is 49.1 cm, width – 28 cm and length – 28 cm, while volumetric image scan is equal to 24.5 cm [92].

In this final research project for the prostate patient daily IGRT was used *Pelvis* scanning protocol (more detailed information about scanning protocol is given in Table 7 and Figure 23). Time of the reconstruction was about 15 s. Delivering time of treatment varied from 5.0 to 6.5 minutes.

Table 7. kV-CBCT *Pelvis* scanning protocol parameters

Mode	Energy keV	Exposure mAs	CTDIvol (mGy)	DLP (mGy*cm)	Scan time (s)	Diameter (cm)	Range (cm)	Matrix (pixel)	Thickness (mm)	iCBCT
Pelvis	125	1080	21.60	324	36.7	49.2	13.2	512	2.0	+

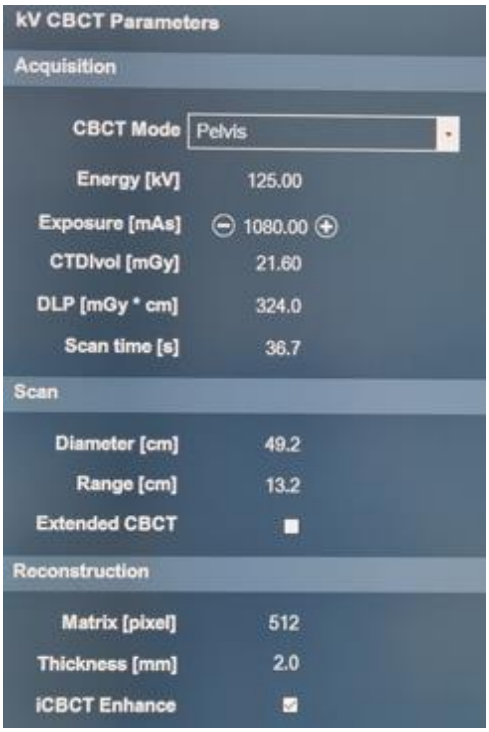


Fig. 25. kV CBCT *Pelvis* scanning protocol

Other imaging technique is computed tomography. Fan beam computed tomography (FBCT) consist of solid-state detector and source of x-ray. These FBCT mechanical parts are fixed on the rotating gantry.

Operating principal of fan beam computed tomography (FBCT) is based on a narrow fan-shaped beam of x-ray which transfers through the patient body (Fig. 24). Source of x-ray moves together with a rotating gantry around the patient. During FBCT scanning procedure patient is "sliced", one image at a time with full 360° range rotation. Scanning is done in helical technique – one step one image. All images are getting by multiple gantry rotations. Then all slices are interpreted, and 2D images are obtained [80, 93].

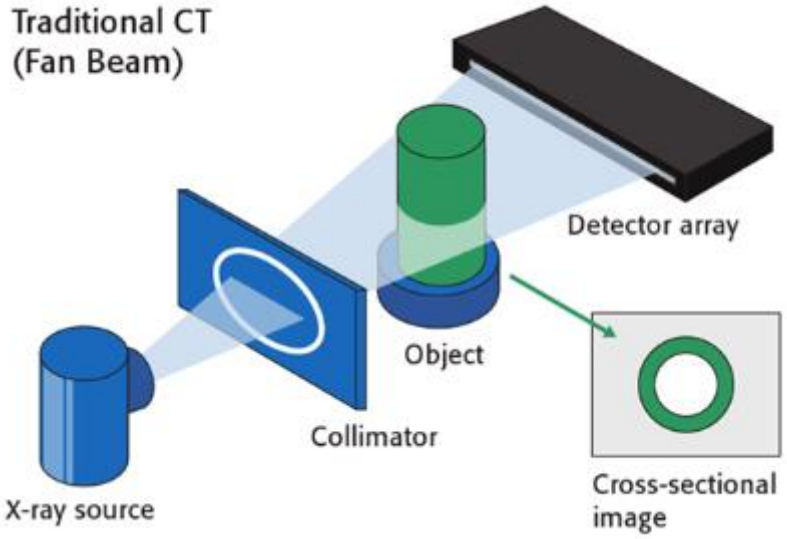


Fig. 26. Fan beam computed tomography operating principle [94]

Comparing FBCT to cone-beam CT, Lechuga and Weidlich [95] results showed that FBCT has a better anatomic visualization, less noise in an image, and a better resolution of low contrast, smaller dose to the patient, and has better uniformity image artifacts than cone-beam CT. But cone-beam CT has a better spatial resolution and can get images with greater volume in a single scan than FBCT. FBCT has a smaller number of sensors, but acquisition of data is faster than in cone-beam CT [95-96].

FBCT has a good visualization of anatomy, that it is important for various tissues and organs due to the difference in density of the materials [96].

2.2. Treatment planning system *Eclipse*

Commercial 3D treatment planning system (TPS) *Eclipse* is created by Varian Medical Systems (Varian Medical Systems, Palo Alto, CA, USA) for radiotherapy purposes (Fig. 25). Features of the TPS *Eclipse*: 3D dose analysis, surface of isodose and dose mapping, also rapid calculations of dose by advanced processor. It allows to visualize strategy of radiotherapy treatment and let to ensure dose coverage of the tumour. The *Eclipse* version 16.1 can be used for many treatment modalities such as electrons, photons, brachytherapy, protons, and even cobalt therapy [97].

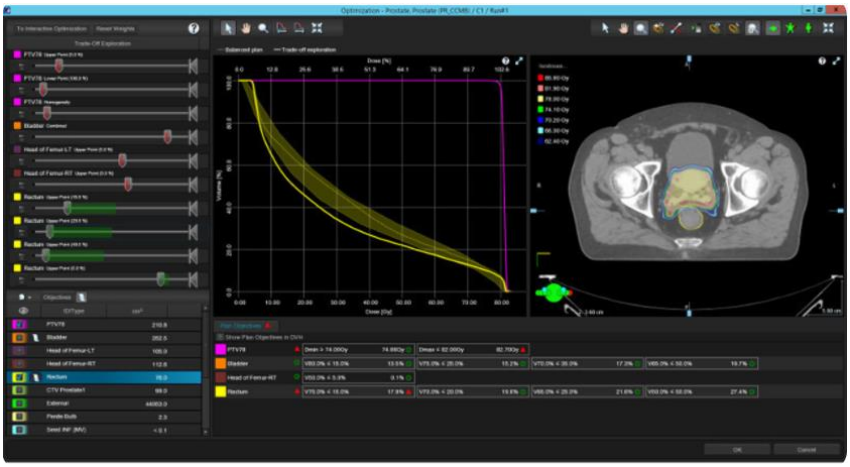


Fig. 27. Treatment planning system *Eclipse* for radiotherapy [98]

TPS *Eclipse* was used to create plans for the prostate cancer planning with IMRTtechnique. Treatment plans for patients with prostate cancer were planned after CT scanning, which must be done before each treatment contouring and planning procedure. CT simulation data sets are all imported to the *Eclipse* system, and here all data are used without medical information loss.

2.2.1. Re-contouring of organs at risk

Rectum and bladder were re-contoured on a daily iCBCT images, which were compared with original/ reference CT images, for the changes of volume evaluation (Fig. 26). Fully were analysed two prostate patients, with the treatment prescribed dose of 80 Gy, 2 Gy/ fraction. All the contours (target and OARs) on a CT images were delineated by the radiation-oncologists, while re-contouring on 40 iCBCT images per one patient was done by author of the final project, with a radiation-oncologist‘s supervision.

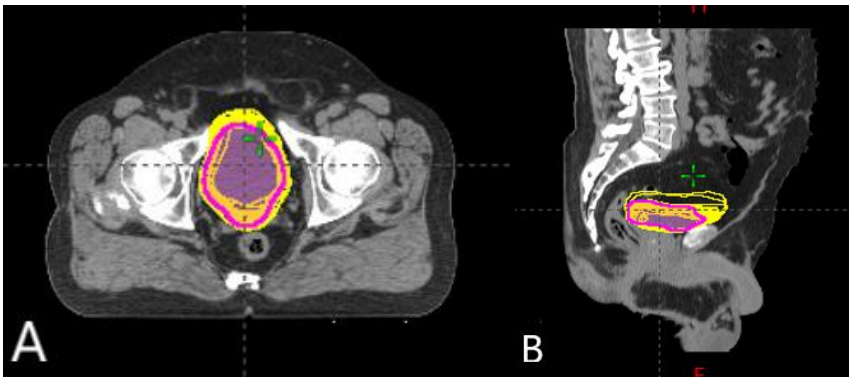


Fig. 28. Reference delineated contour of bladder on CT scans (purple)

Rectum and bladder recontouring were done according to a patient anatomy of the irradiation day. After the contouring procedure treatment planning of the patient were done.

2.2.2. Computed tomography number dependence on physical density and electron density curves measurement

Phantom *Gammex 467* was used for computed tomography number dependence on physical density (CT-PD) and electron density (CT-ED) curves measurement (Fig. 27).

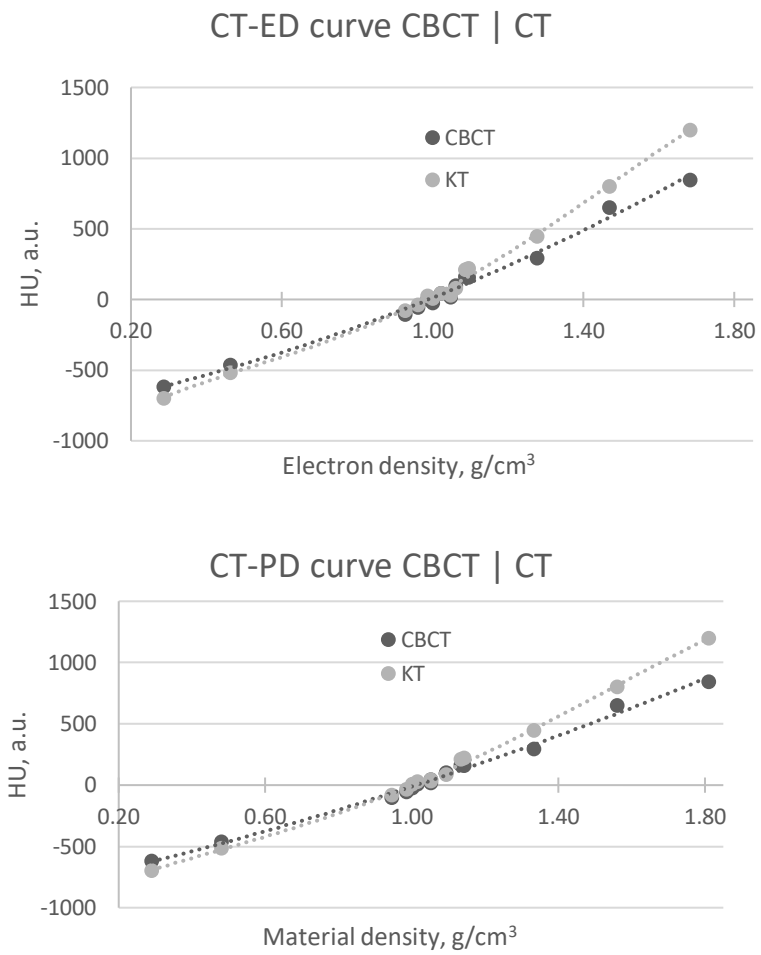


Fig. 29. Density and HU values graphs, obtained with LA *Halcyon*

Phantom *Gammex 467* have different rods/ insertions of various materials (Fig. 28 and Table 8).

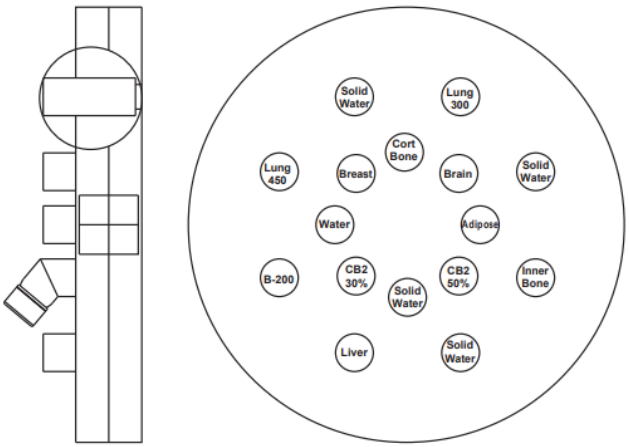


Fig. 30. *Gammex 467* cross section view [99]

Table 8. Characteristics of different insert in *Gammex 467* [99]

Rod Materials	Physical density, g/cm^3	Electron density relative to water, g/cm^3	HU
LN-300 Lung	0.290	0.286	-613
LN-450 Lung	0.480	0.463	-455
AP6 Adipose	0.944	0.927	-147
BR-12 Breast	0.984	0.961	-130
Water Insert	1.000	1.000	-83
CT Solid Water1	1.015	0.986	-25
CT Solid Water2	1.015	0.986	60
CT Solid Water3	1.015	0.986	43
CT Solid Water4	1.015	0.986	100
BRN-SR2 Brain	1.052	1.048	157
MS11 Muscle	1.052	1.021	163
LV1 Liver	1.093	1.061	292
IB Inner Bone	1.134	1.087	530
B200 Bone Mineral	1.142	1.095	676
CB2-30% CaCO3	1.332	1.277	-
CB2-50% CaCO3	1.559	1.469	-
SB3 Cortical Bone	1.810	1.683	-
Titanium Grade 2	4.590	3.790	4856
316 St Stl	8.000	6.580	5169

Different density rods are important to evaluate relationship between density of electrons in various tissues, and their responding in Houndfield Units/ CT numbers, simulating various scattering cases (Fig. 29). The size of the phantom is similar to an average pelvis, diameter is 33 cm, diameter of holes – 2.8 cm.

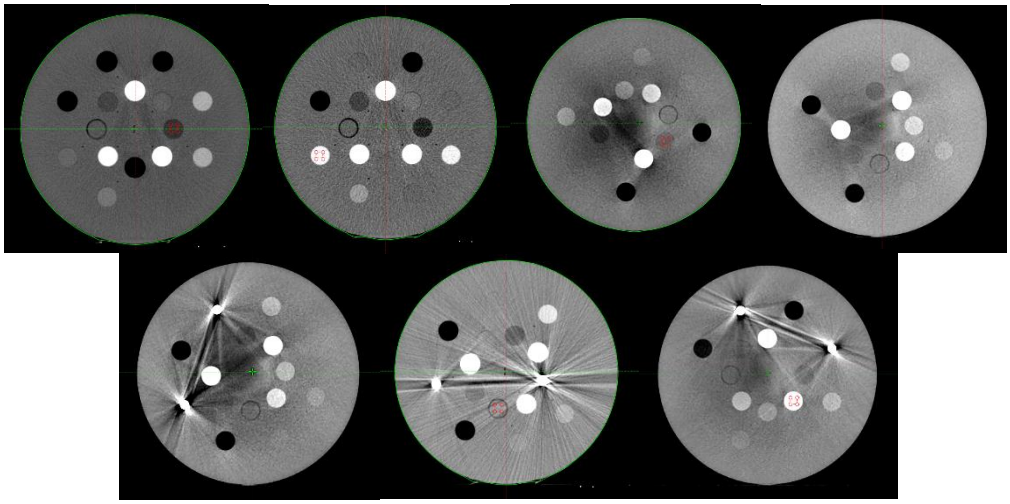


Fig. 31. Various scattering cases analysis using different densities of the inserts in a Phantom *Gammex 467*

Also, a good quality of CBCT images can be improved with modifications in scanning protocols. For example, higher parameters of mAs give better quality than lower but it also, gives higher dose. Slice thickness affects a contrast of soft tissues, and etc. [100].

2.3. Treatment planning of prostate patient and planned treatment plans evaluation of the main dosimetry data

The studied patients were planned using inverse treatment planning techniques called intensity modulated radiotherapy (IMRT) (Fig. 30). Prescribed dose to the target for the PTV was 50 Gy, 2 Gy per fraction, and to the Boost plan prescribed dose was equal to 30 Gy, 2 Gy/ fr.

PTV plan is initial plan (standard) for the patient for prostate cancer, and plan is based on tumour size, location, type, the number of lymph nodes with cancer, includes OARs etc. PTV usually prescribed dose to patient is 50 Gy. While, after initial plan for the patient a given a Boost plan. It is plan which focused on the primary tumour location. The Boost plan increases amount of the ionizing radiation dose and reduce local recurrence risk. The sessions of the Boost treatment are the same as initial plan. All treatment periods include 25 fractions of initial plan PTV and 15 fractions of the Boost plan.

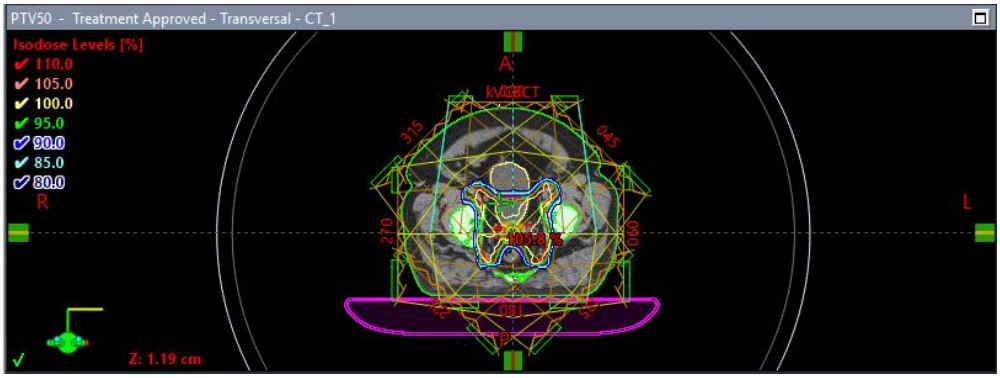


Fig. 32. IMRT plan for prostate cancer

The main geometry of the fields is presented in a Figure 30. It could be seen that 8-field geometry (0º, 45º, 90º, 135º, 180º, 225º, 270º, 315º) was used for the treatment plan planning. 6 MeV FFF energy was used for the treatment planning. All the plans were firstly planned on a reference CT images, and later on re-copied with the same parameters on daily iCBCT scans.

All the plans were evaluated regarding the clinical goals tables (Fig. 31 and Fig. 32). Clinical goals used to estimate the bladder dose is 50 % < 50 Gy, 70 Gy < 35 %, 80 Gy < 15 %. It means that the indicated volume should not exceed the stated dose recommendations. For rectum dose evaluation are used these clinical goals 50 Gy < 50 %, 60 Gy < 25 %, 70 Gy < 20 % and 75 Gy <15 %.

Clinical Goals

Plan			Σ - Plan Sum
Total Dose			N/A
Clinical Goal Summary			3 1 15
CTVboost	P1	D 99.0 % > 80.00 Gy	80.05 Gy
PTVboost	P1	D 99.0 % > 47.50 Gy	76.91 Gy
	P1	D 99.0 % > 76.00 Gy	76.91 Gy
	P1	D 1.0 cm³ < 84.00 Gy	83.76 Gy
AnalCanal	P4	Dmean < 40.00 Gy	38.42 Gy
Bladder_PTV_0	P2	D 50.0 % < 50.00 Gy	59.21 Gy
	P2	V 70.00 Gy < 35.0 %	24.01 %
	P2	V 80.00 Gy < 15.0 %	9.67 %
Bowel_Small	P4	D 195.0 cm³ < 45.00 Gy	17.03 Gy
Femur_L	P3	Dmax < 52.00 Gy	48.90 Gy
Femur_R	P3	Dmax < 52.00 Gy	48.34 Gy
Rectum_PTV_0	P2	V 50.00 Gy < 50.0 %	48.70 %
	P2	V 60.00 Gy < 35.0 %	18.23 %
	P2	V 65.00 Gy < 25.0 %	8.95 %
	P2	V 70.00 Gy < 20.0 %	4.43 %
	P2	V 75.00 Gy < 15.0 %	2.73 %

Fig. 33. Clinical goals table for the bladder and rectum dose estimation

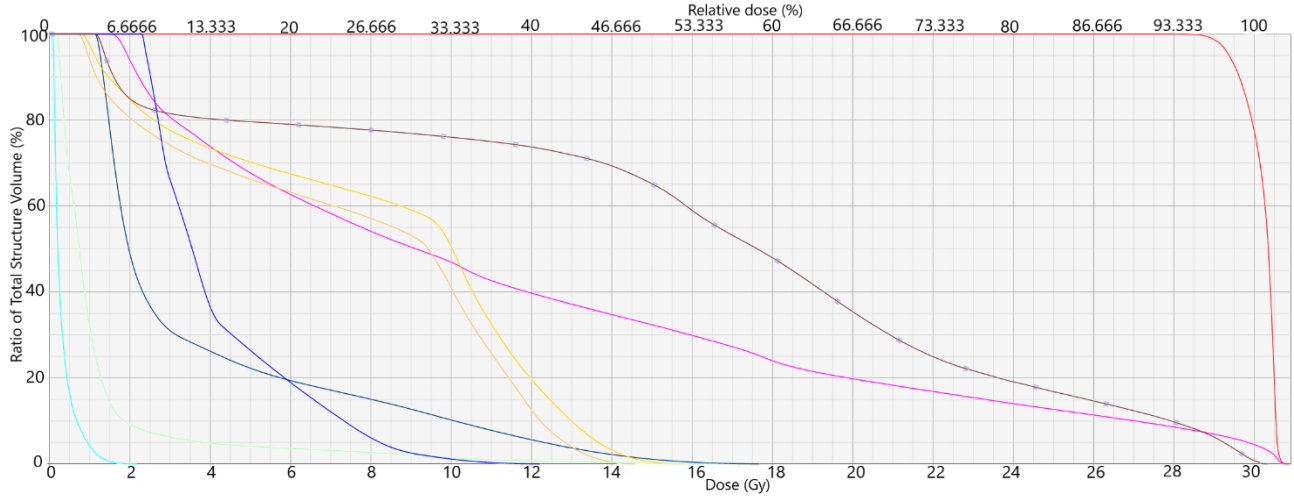


Fig. 34. Dose-volume histogram of OARs

3. Results

All the research process was divided into two main parts: 1) were analysed how the changes the volumes of bladder and rectum during daily treatment procedure, and 2) were planned and compared treatment plans planned on CT and daily iCBCT scans. Therefore, regarding the contouring and planning results were prepared the main recommendations of the usage of iCBCT for the prostate cancer patient.

3.1. Analysis of delineated target and organs at risk volume changes

Target volumes - planning target volume (PTV) and clinical target volume (CTV), and organs at risk (bladder and rectum) on cone-beam computed tomography (CBCT) scans were re-copied from the reference CT scans. Changes of target volumes were not significant in comparison with a reference CT scans (in Table 9 and Appendix 1), because target volumes were not adapted regarding the possible changes of the treatment volume during the patient treatment.

Table 9. PTV and CTV volumes compared with PTV50 (reference) volume

	Structure	PTV50	Mean value of CBCT	Max value of CBCT	Min value of CBCT	SD*
Patient 1	PTV	1844.7	1844.5	1845.9	1840.7	1.3
	CTV	1267.2	1267.2	1268.9	1265.3	1.0
Patient 2	PTV	645.9	641.3	644.1	639.5	1.0
	CTV	314.7	310.5	313.3	309.1	1.0

*SD – standard deviation

Analysis of organs at risk volume (bladder and rectum) changes were significant in comparison with a delinated structures on reference CT scans (Fig. 35). These OARs are the organs at risk, which volumes are changable naturally due to bladder or rectum filling. It means that volume vary from day to day. Due to this reason, the IGRT allows to follow these changes and make on-line corrections. Re-contouring of OARs volumes was done on CBCT images. The main differences of these volumes are presented in a Table 10 and Figure 33.

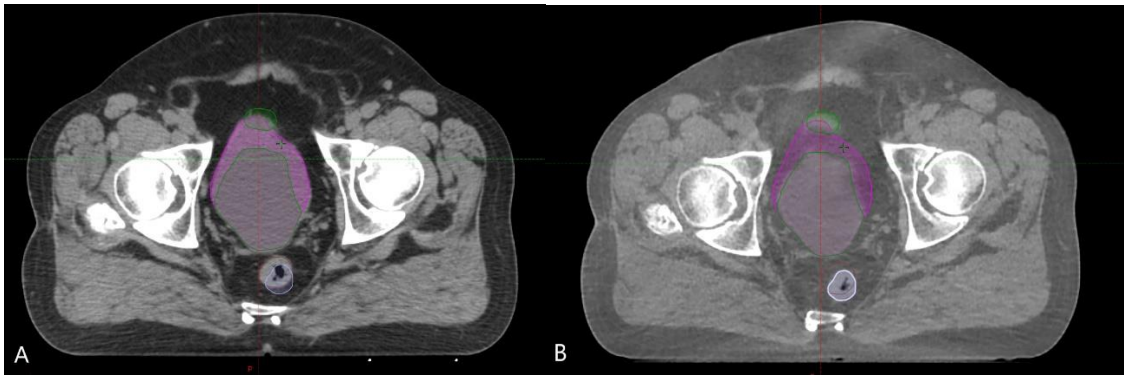


Fig. 35. A – CT image with reference line of the rectum (purple colour), B – iCBCT image with rectum line (purple colour)

Table 10. Planning CT and daily CBCT mean, minimum and maximum values

	CT	**Daily CBCT bladder volumes (cc)**		
	Bladder			
	CT bladder volume (cc)	Mean	Minimum	Maximum
Patient 1	166.8	160.4	64.5	319.0
Patient 2	126.3	125.9	55.4	298.8
	Rectum			
	CT rectum volume (cc)	Mean	Minimum	Maximum
Patient 1	83.1	87.9	49.5	148.3
Patient 2	35.7	50.7	38.2	107.9

It was observed that for the Patient 1 volume changes varies more in comparison with a Patient 2. It means that it is very important for the future analysis to study more patient cases, evaluating as larger amount of data as possible. Therefore, it was noticed that the bladder volume of Patient 1 has 1 outlier, which value was equal to 319 cc, while Patient 2 has 2 outliers – 298.8 cc and 265.9 cc (Fig. 36). The same tendency of results was observed, and for the changes of rectum volume. It is known that outliers usually show higher differences between studied issues, for example, volumes. It is known that differences could occur due to different bladder/rectum filling. Bladder filling comparison by Pearson et al. [101] showed that a daily CBCT bladder volume in compare with planning CT differed from 76.16 cc to 380 cc (reference bladder volume on CT scans was equal to 470.6 cc). Arya et al. [102] study also confirmed significant bladder volume variations during all the treatment period.

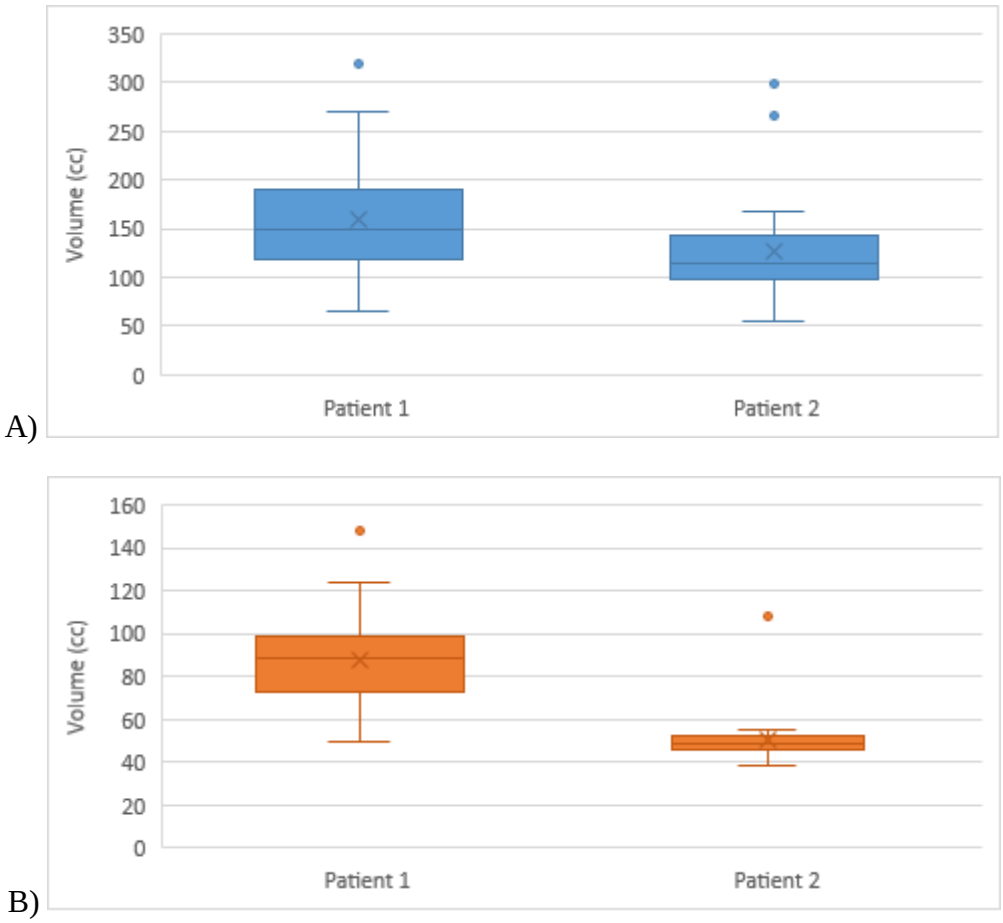


Fig. 36. Patient 1 and Patient 2 mean, maximum and minimum values of bladder (1) and rectum (2) volume changes with evaluated outliers

All the bladder and rectum contours on a daily iCBCT scans were put together in one plan, showing how the volume of the bladder changes during daily iCBCT procedure compared with the reference contour for Patient 1 and Patient 2 (Figure 37 and Figure 38).

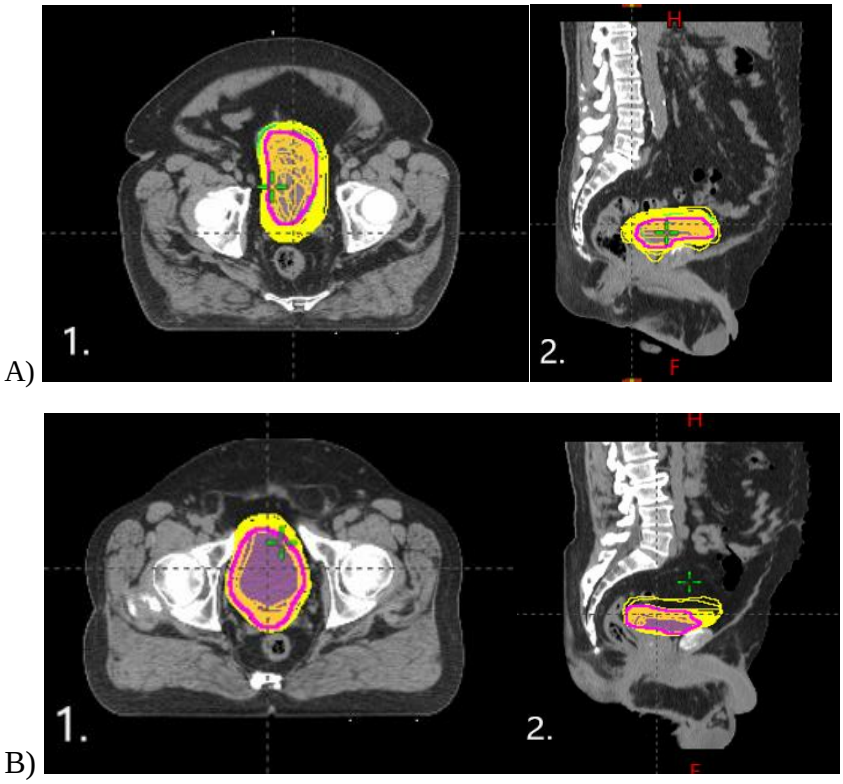


Fig. 37. A) Patient 1 and B) Patient 2: 1 – bladder volume differences in transversal axis, 2 – bladder volume changes in sagittal axis (yellow colour). The reference contour of the bladder is visualised in pink colour

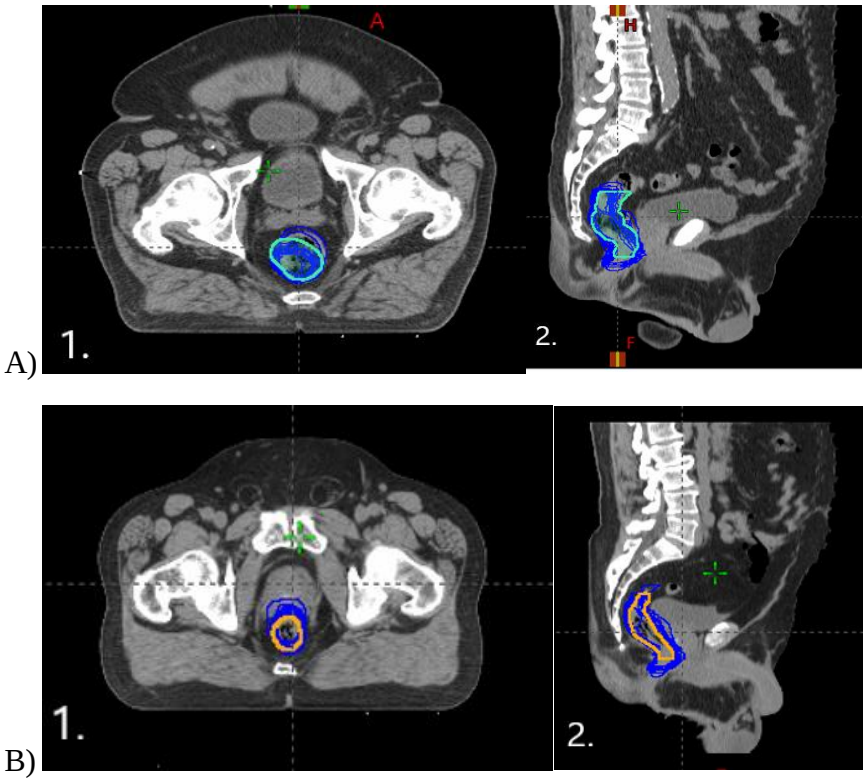


Fig. 38. A) Patient 1 and B) Patient 2: 1 – rectum volume differences in transversal axis, 2 – rectum volume changes in sagittal axis (dark blue). Reference contour of the rectum is visualised in orange colour

Analysis of the ourliers showed that it could occur due to a largst volume changes of analysed delineated structures in comparison with a refererence CT scans. Due to this reason, different volume variations of the rectum could occur due to excrement quantity and formed air bubbles, while, bladder volume variations occur due to different amount of filling. It could happen, because, for example, some patients are too nervous and could drink more water before the treatment procedure, the bladder becomes full, and the patient holds the urine or some patients are more relaxed and feel uncomfortable, if drink more water before the radiotherapy procedure, and etc. Moreover, Patient 1 bladder volume changes were uneven with larger volume differnces throughout the treatment period, while rectum volume changes were observed without major changes, while for Patient 2, greater changes in a bladder volume occurred only during the first fractions of the first treatment week, after which the volume remained fairly constant, while rectum volume changes remains little changed (Fig. 39 and Fig. 40).

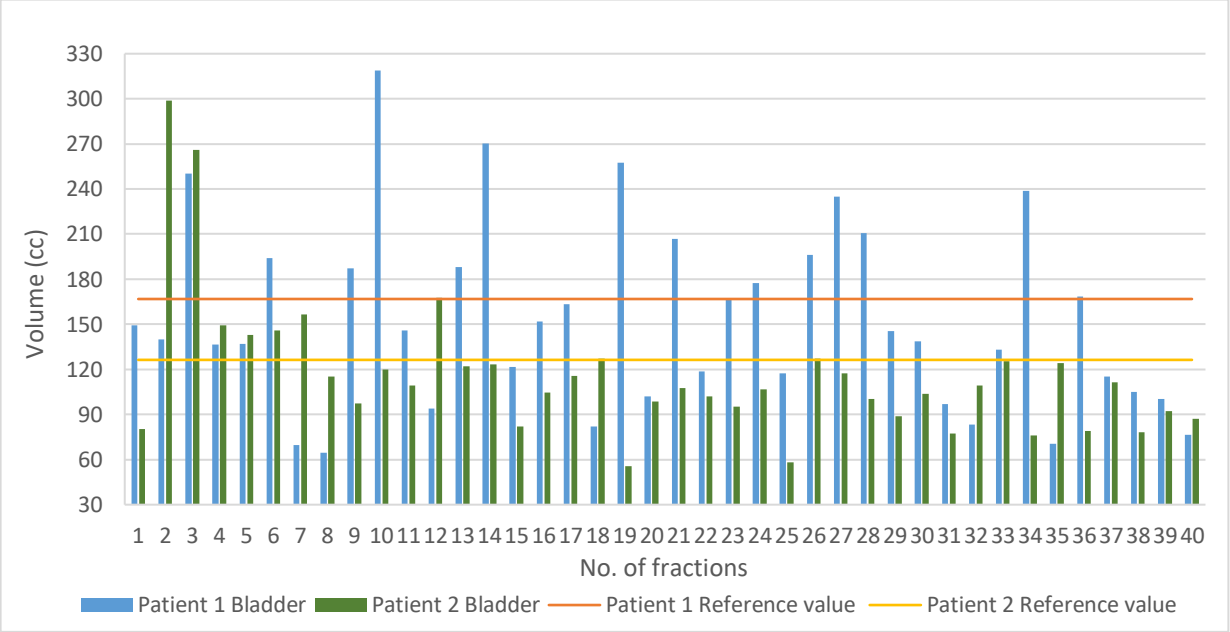


Fig. 39. Changes of bladder volume for Patient 1 and Patient 2

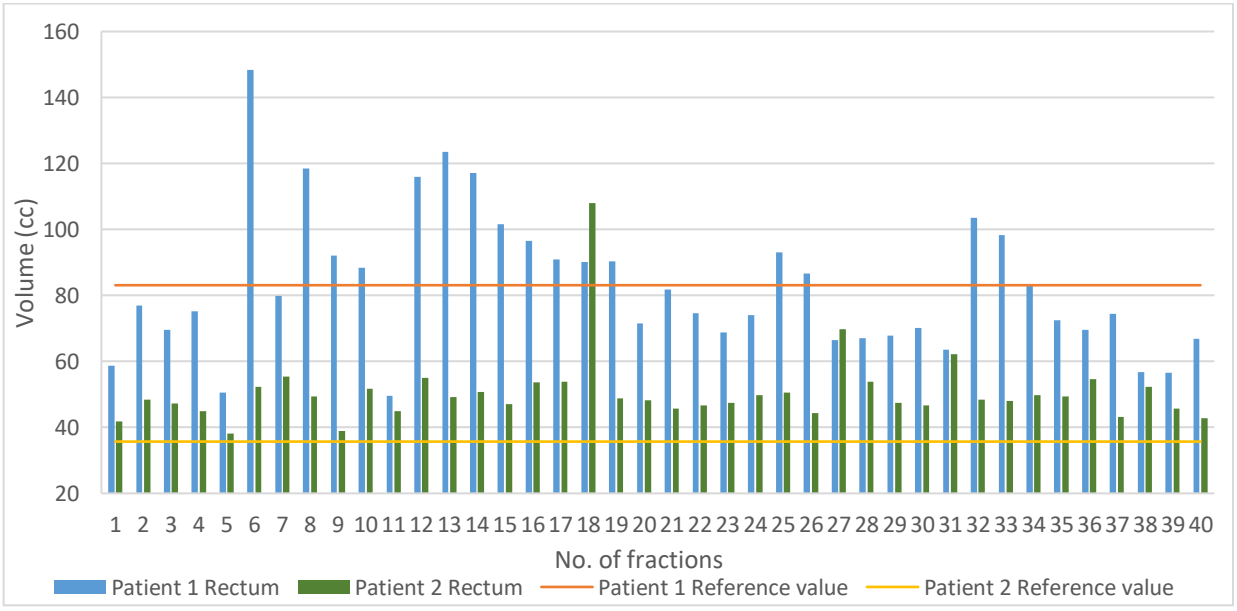


Fig. 40. Volume variations of bladder and rectum for Patient 1 and Patient 2

3.2. Evaluation and comparison of the dosimetry data for the treatment plans planned on computed tomography and cone-beam computed tomography scans

Volume effect analysis. The reference treatment plans for both prostate cancer patients (Patient 1 and Patient 2) were planned on CT scans and copied on a daily iCBCT scans, analysing the main differences, and comparing the final results planning on CT and iCBCT. The irradiation doses for the both patients received by the target and OARs (bladder and rectum) were estimated by dose-volume histograms (DVH) (Fig. 41 and Fig. 42).

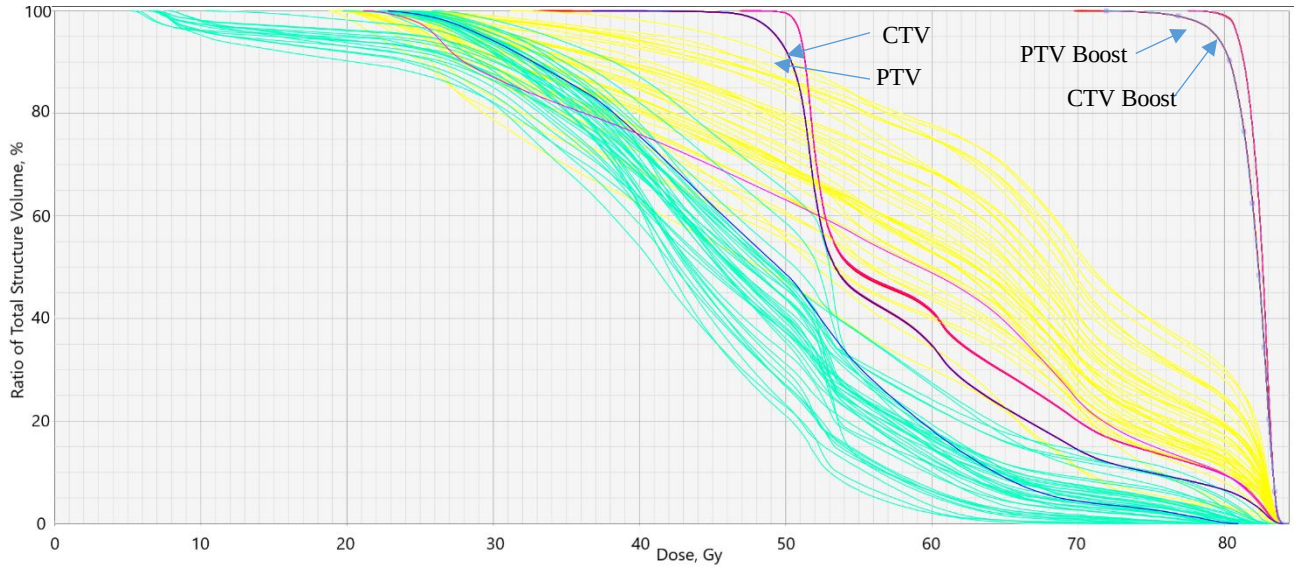


Fig. 41. Patient 1: doses of CTV (red lines, reference – purple) and CTV Boost (red lines, reference – dark purple), PTV (red lines, reference – dark blue) and PTV Boost (red lines, reference – light blue), bladder (yellow lines, reference – purple), rectum (light blue lines, reference – dark blue)

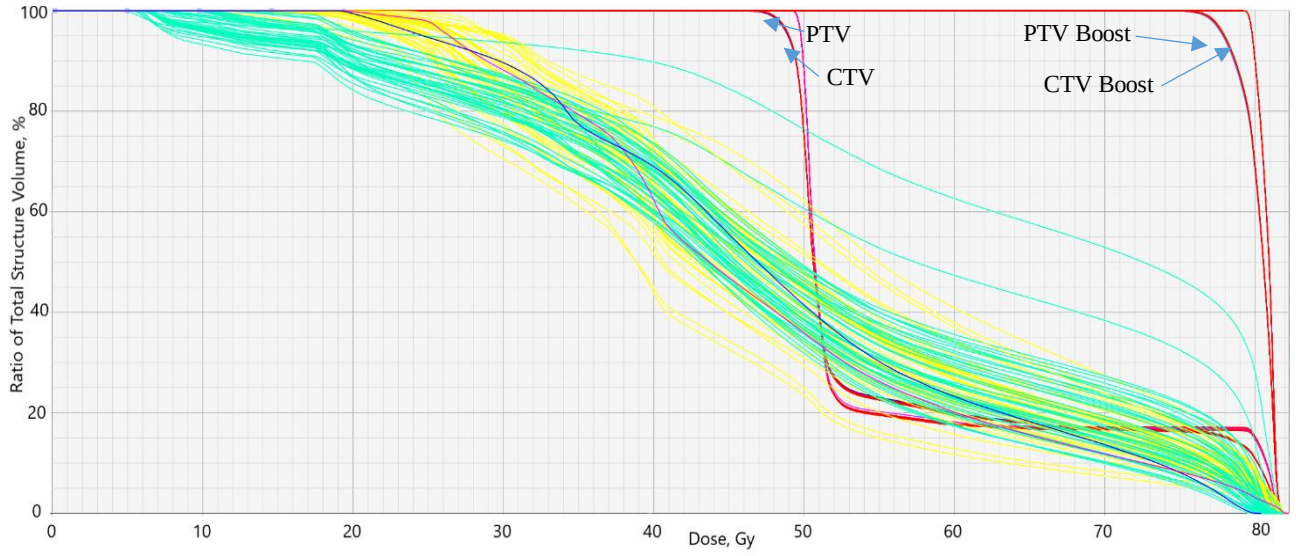
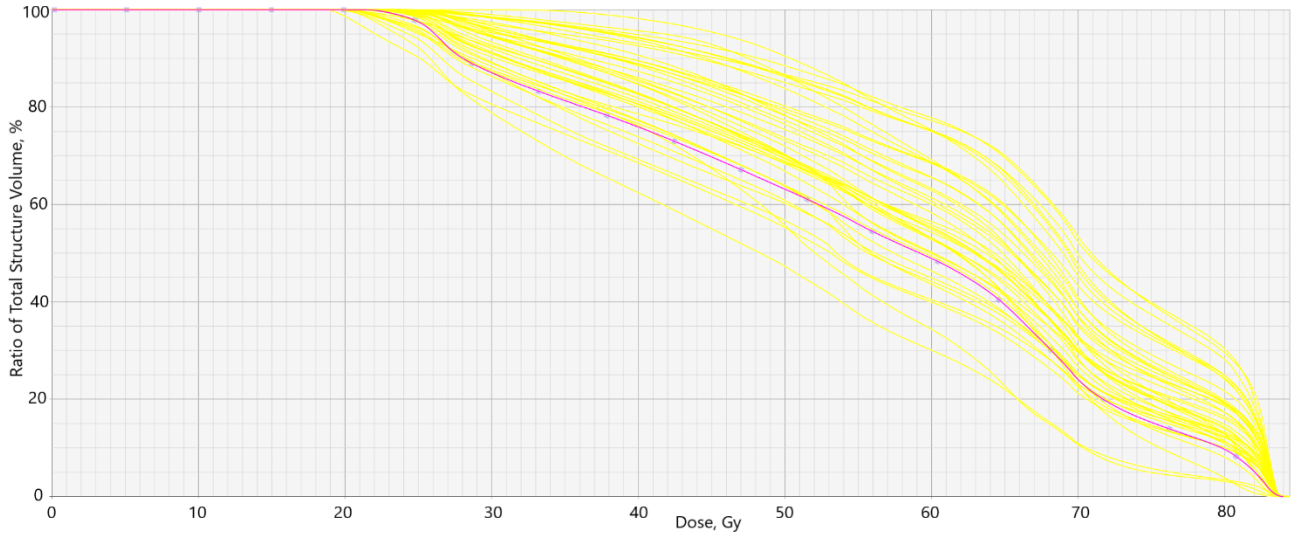


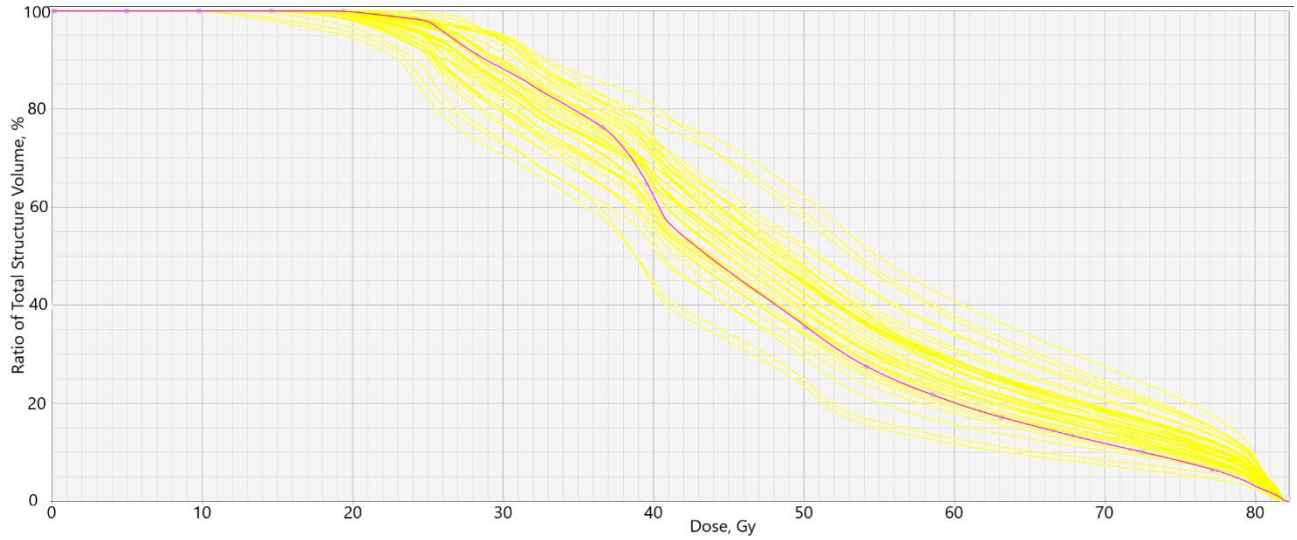
Fig. 42. Patient 2: doses of CTV (red lines, reference – purple) and CTV Boost (red lines, reference – dark purple), PTV (red lines, reference – dark blue) and PTV Boost (red lines, reference – light blue), bladder (yellow lines, reference – purple), rectum (light blue lines, reference – dark blue)

It was observed that DVH curves of target volumes (PTV, CTV, PTV Boost, and CTV Boost) were similar and differed not significantly, because any changes of these volumes were not performed, they were just re-copied fron CT plan. Comparison CT and CBCT planning of bladder and rectum irradiation

doses were analysed by Pearson et al. [101]. It was observed that an average volume of the bladder was smaller for 74.7 % planning on a daily CBCT. Also, was found that for one patient bladder volume was smaller planning treatment on a daily CBCT during whole treatment period. Analysis of final research project results (Patient 1 and Patient 2) showed that for the bladder of Patient 1 2.5 % of all with iCBCT planned treatment plans were in a good agreement with clinical goals (50.0 % < 50.00 Gy; 70.00 Gy < 35.0 %; 80.00 Gy < 15.0 %), and 97.5 % (Patient 1) were slightly higher than it is recommended (Fig. 43 A) and B)), while analysis of the Patient 2 showed that 12.5 % were in a good agreement with dose constraints, and 87.5 % out of recommended limits. It means that Patient 2 bladder changes in comparison with a Patient 1 differed per 10 %. These results shows that changes of the bladder volume are dependent on a patient, and has to be followed individually.



A)

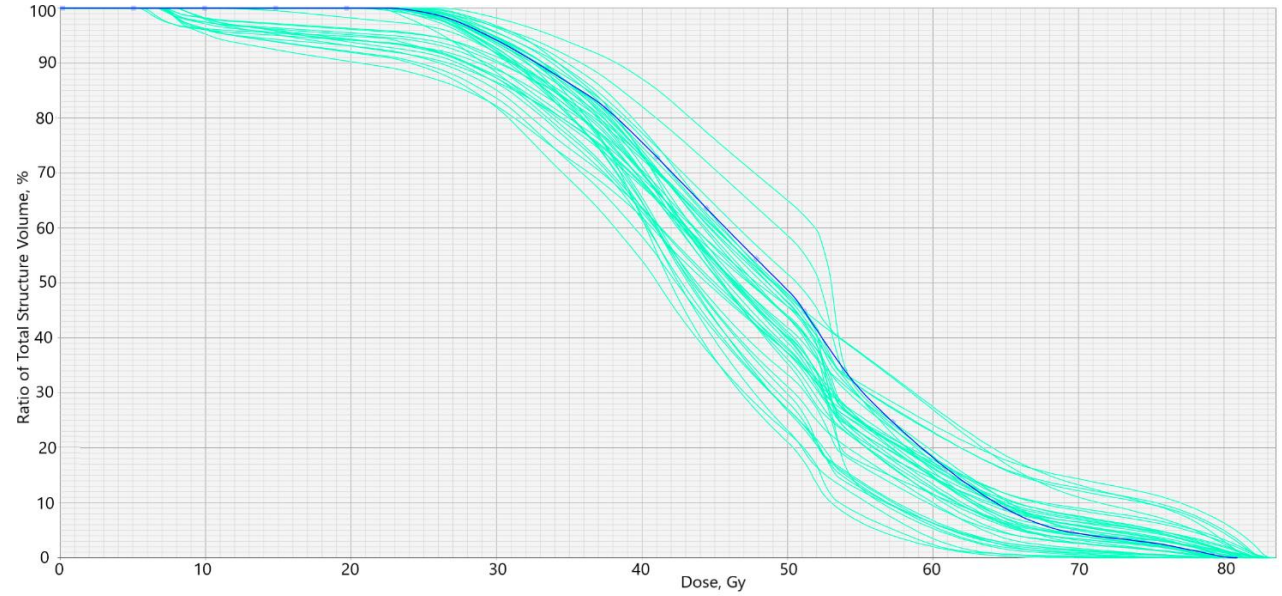


B)

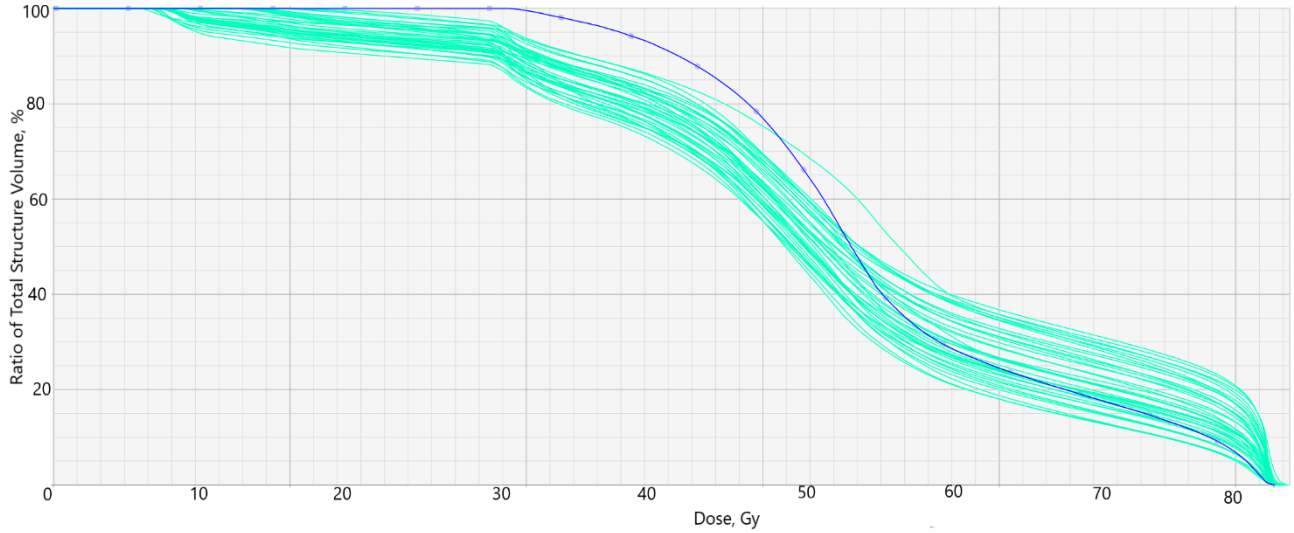
Fig. 43. A) Patient 1 and B) Patient 2: bladder PTV50 and Boost treatment plan lines noted in yellow colour, reference line – purple colour

Therefore, evaluating possible changes of bladder volume during daily iCBCT could be really valuable reducing the toxicity of the patient. The same tendency of the results also was observed in a study of

Gurjar et al [5]. It was found thatlarger volume of the bladder in comparison with the first CT scanning of the patient can shift the prostate to posterior direction, due to this reason daily CBCT allow to follow the changes of the bladder volume, and minimizing toxicity of healthy tissues and critical organs. To control the volume changes of bladder is really difficult and challengable step, but it is known that some adjustments can be made, for example, by applying a water filling protocol [103]. Almost the same tendency was observed analysing volume changes of rectum for both patients. It was observed that 92.5 % (Patient 1) and 42.5 % (Patient 2) of all iCBCT planned treatment plans were in a good agreement with clinical goals (50.00 Gy < 50.0 %; 60.00 Gy < 25.0 %; 70.00 Gy < 20.0 %; 75.00 Gy < 15.0 %) for the rectum, while 7.5 % (Patient 1) and 57.5 % (Patient 2) were slightly higher than it is recommended (Fig. 44 A) and B)). The same tendency of the were observed and in Fuchs et al. [104] study. It was showed that correlation between mean dose and rectum volume changes is not so significant in comparison with changes of bladder volume. It is known that air bubbles and faeces is main factors affecting the rectum volume and it is uncontrollable processes [104].



A)

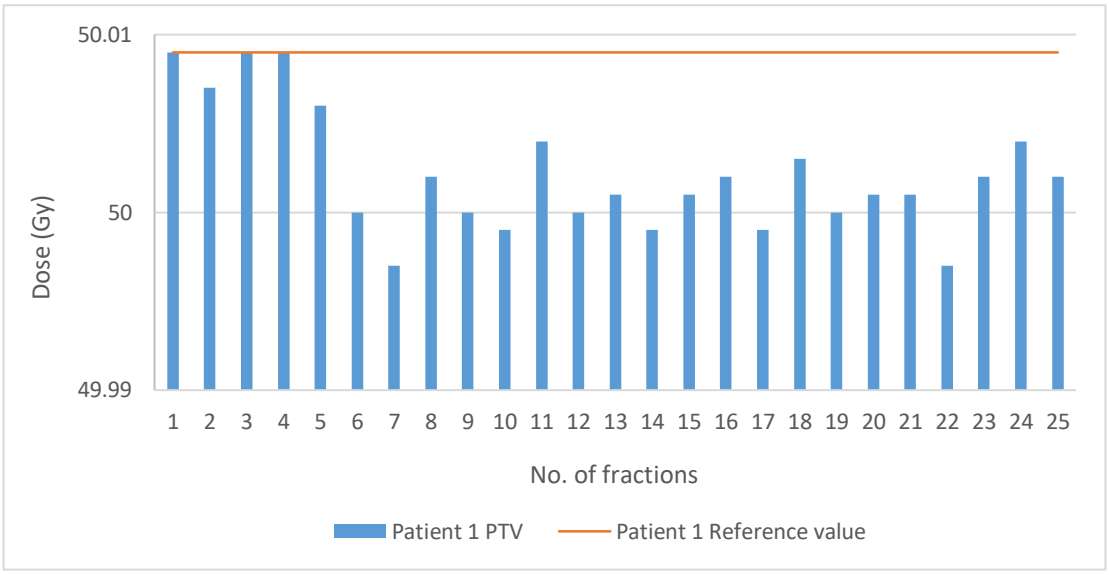


B)

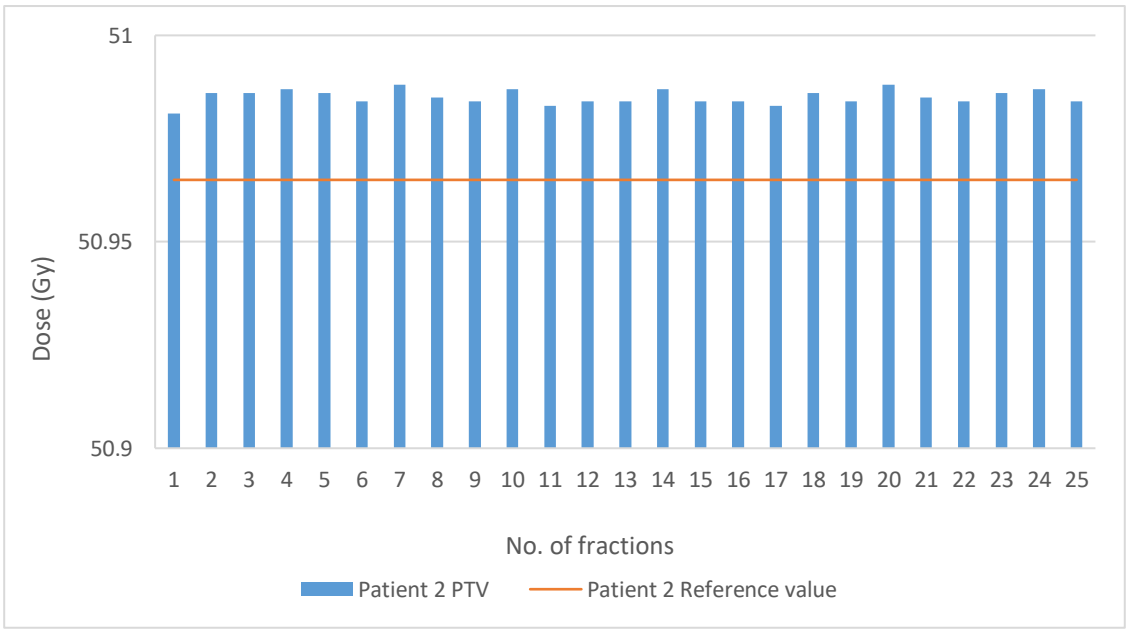
Fig. 44. A) Patient 1 and B) Patient 2: rectum PTV50 and Boost treatment plan lines noted in light blue colour, reference line in dark blue

Therefore, volume changes during the radiotherapy course is very complex issues. Chen et al. study [105] showed that if bladder volume increases by 10 %, the mean dose for the bladder could be reduced by 5.6 % .

Differences of CT and iCBCT treatment plans analysis. The main dosimetry data of the target volume (PTV) for both patients (Patient 1 and Patient 2) are presented in a Figure 45 and Figure 46.

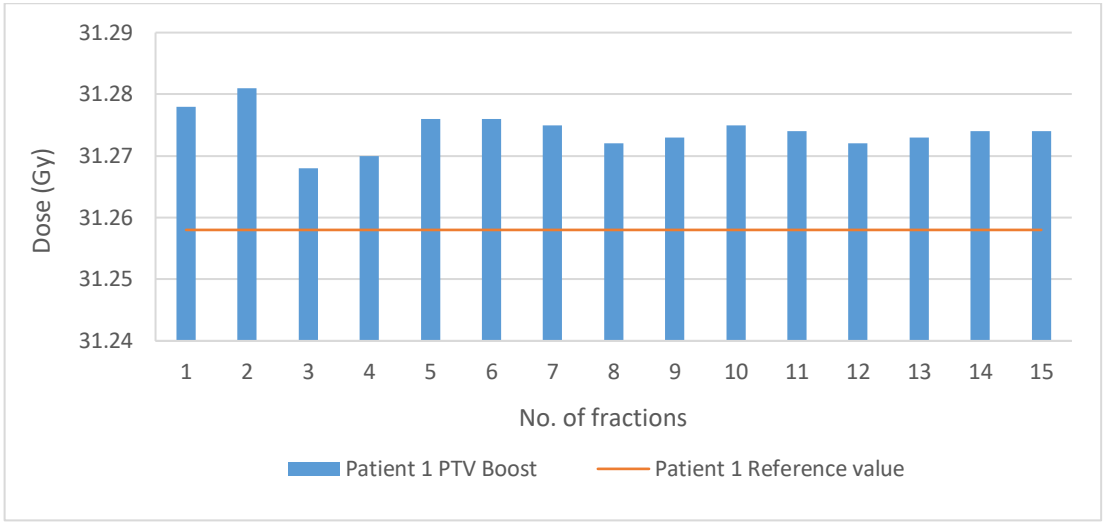


A)

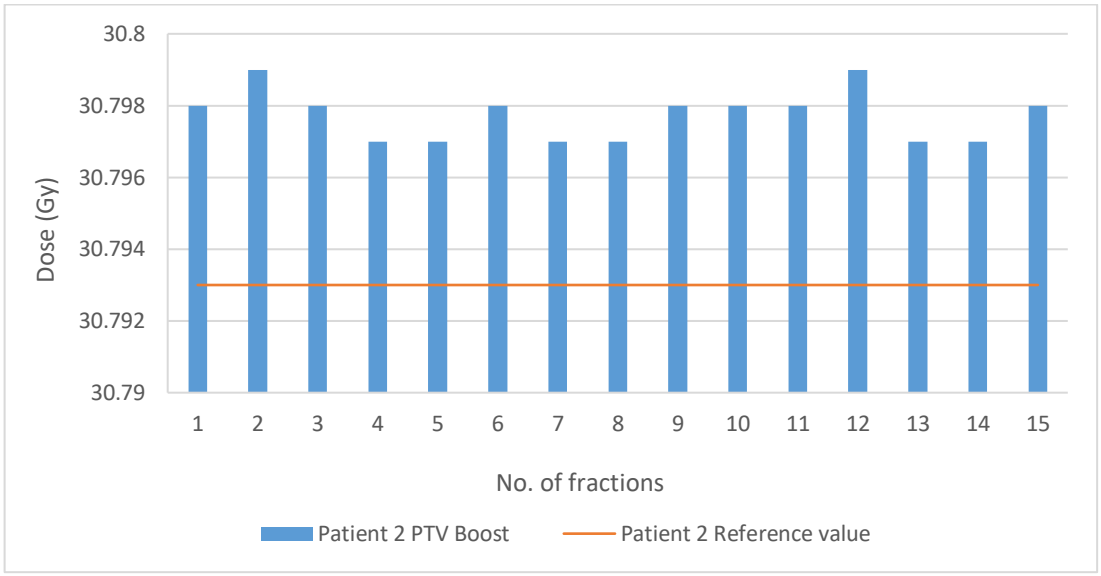


B)

Fig. 45. Mean PTV doses of Patient 1 (A) and Patient 2 (B). Orange line is a reference value (CT)



A)



B)

Fig. 46. Mean PTV Boost doses of Patient 1 (A) and Patient 2 (B). Orange line is reference value (CT)

It was found that the reference value of the mean dose on CT for Patient 1 was equal to 50.009 Gy/ 100.02 % (PTV) and 31.258 Gy (Boost)/ 104.2%, while for Patient 2 – 50.965 Gy/ 101.93 % (PTV) and 30.793 Gy (Boost)/ 102.6 %. It means that requirements of the coverage are fulfilled fully, while it is known, that the prescribed dose has to differ from 95% to 107%. Re-calculating the main differences between target volumes planned on CT and iCBCT was found that PTV coverage differed in between from 0.00 % to 0.02 % (Patient 1) and from -0.03 % to -0.05 % (Patient 2), while Boost coverage differed from -0.03 % to -0.07 % (Patient 1) and from -0.01 % to -0.02 % (Patient 2). It means that planned dose with CT and iCBCT is in good agreement and have very slight defferences. Analysing Jarema et al. [87] study results were determined that mean dose difference of PTV between pCT and iCBCT differed -1.2 % (Patient 1), -0.2 % (Patient 2), -1.7 % (Patient 3), 0.1 % (Patient 4), 0.2 % (Patient 5) The differences are really negligible and show a good agreement between planning on CT and iCBCT. It means that treatment planning for the prostate patient using daily iCBCT is really promising and encouraging using it for the treatment planning, evaluating possible target volumes and/ or critical organs movement and volume changes.

Conclusions

1. Daily kV-iCBCT imaging and contouring in iCBCT scans visualized changes of bladder and rectum volumes. It was found that due to rectum/bladder filling volumes could be significantly different before each irradiation procedure, as well as between the patients. Changes of the bladder volume differed from the reference CT plan for the Patient 1 – 3.8 % (with 319 cc outlier), while for the Patient 2 – 0.3 % (with 298.8 cc and 265.9 cc outliers). The same tendency for both patients were observed for the changes of the rectum volumes – Patient 1 (14.0 %; with 148.3 cc outlier); Patient 2 (5.8 %; with 107.9 cc outlier).
2. Dosimetry analysis of the planned treatment plans on CT and iCBCT showed really good agreement for the target volumes coverage in between. PTV coverage differed from 0.00 % to 0.02 % (Patient 1) and from -0.03 % to -0.05 % (Patient 2), while Boost coverage differed from -0.03 % to -0.07 % (Patient 1) and from -0.01 % to -0.02 % (Patient 2). These results showed that iCBCT could successfully be used for the treatment planning if pelvis region, for example, prostate cancer patient, is planned.
3. Evaluation of the results showed that iCBCT planning (due to a high accuracy) could be successfully used for the pelvis region planning or re-planning for example, for the adaptive radiotherapy, while it allows to contour and follow all the changes in the target and critical structures volumes, estimating the dose to the target and different organs at risk. Due to this reason iCBCT planning for the prostate patient could be used in a clinical practice, especially if it is not used any protocol of bladder or/and rectum filling observation.

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Appendices

Appendix 1. PTV, CTV, bladder and rectum volumes in PTV50 and PTVBoost plans

Table P. PTV, CTV, bladder and rectum volumes in PTV50 and PTVBoost pl ans of Patient 1 and Patient 2

CT and fraction number of CBCT	**Patient 1**				**Patient 2**			
	PTV	CTV	Bladder (cc)	Rectum (cc)	PTV	CTV	Bladder (cc)	Rectum (cc)
PTV50	1844.7	1267.2	166.8	83.1	645.9	314.7	126.3	35.7
1	1844.1	1267.8	149.5	58.6	644.1	313.3	80.4	41.8
2	1844.3	1266.1	140	77	639.8	311.3	298.8	48.5
3	1844.6	1265.3	250.4	69.5	640.4	311.2	265.9	47.2
4	1845.7	1266.2	136.6	75.1	640.7	311.1	149.4	44.9
5	1840.7	1268.3	136.9	50.6	641.8	309.9	142.7	38.2
6	1845.3	1267.1	194.1	148.3	642.1	309.4	145.7	52.2
7	1843.8	1268	69.5	79.8	640.4	311	156.6	55.3
8	1843.4	1267.9	64.5	118.4	642.2	309.3	115.3	49.4
9	1845.5	1266.6	187	92	642	309.3	97.3	38.9
10	1843.3	1268.3	319	88.3	639.8	311.2	120	51.7
11	1845.3	1266.7	146	49.5	641.9	310.2	109.1	45
12	1842.9	1268.9	93.9	115.9	641.3	310.7	167.4	55
13	1844.4	1267.7	188.1	123.6	641.7	310.3	122.2	49.1
14	1843.5	1268.5	270.3	117.2	641.3	310.5	123.5	50.7
15	1843.7	1268.2	121.7	101.6	642.1	309.1	81.8	47
16	1845.8	1266.7	151.7	96.5	641.5	310.5	104.4	53.6
17	1843.4	1268.5	163.5	91	642.2	309.6	115.8	53.9
18	1845.8	1265.8	81.9	90.1	639.5	311.3	127.2	107.9
19	1843.8	1268.1	257.6	90.4	642	309.2	55.4	48.8
20	1845.7	1266.5	102	71.6	640.7	310.7	98.4	48.2
21	1844.8	1267.2	206.9	81.7	641	310.8	107.7	45.7
22	1845.2	1267.2	118.7	74.6	642.1	309.5	102.2	46.6
23	1845.8	1267.1	166.4	68.7	639.8	311.5	95.4	47.4
24	1845.8	1265.3	177.3	74	641.5	310.4	106.5	49.8
25	1845.9	1266.5	117.5	93	641.2	310.8	58	50.6
	PTV	**CTV**	**Bladder (cc)**	**Rectum (cc)**	**PTV**	**CTV**	**Bladder (cc)**	**Rectum (cc)**
PTV Boost	111.6	48.9	166.8	83.1	102.4	51.6	126.3	35.7
1	110.7	48.6	196.2	86.7	101.7	51.3	127	44.4
2	110.3	48.8	235.1	66.4	101.8	51.4	117.5	69.7
3	111.3	48.3	210.8	67	101.9	51.4	100.1	53.9
4	111.1	48.2	145.6	67.8	102.1	51	89	47.4
5	110.8	48.6	138.7	70.1	102.1	50.9	103.8	46.7
6	110.8	48.6	97.1	63.5	101.9	51.4	77.4	62.2
7	110.7	48.6	83.4	103.5	102.1	51.1	109.1	48.4
8	111.1	48.6	133.3	98.2	101.9	51.2	125.4	48.1
9	110.9	48.1	238.7	83	102	51.1	76.2	49.7
10	110.5	48.5	70.6	72.4	101.9	51.4	124.3	49.4
11	111.1	47.9	168.4	69.6	101.9	51.3	78.8	54.6
12	111.1	48.1	115.2	74.5	101.9	51.1	111.2	43.2
13	111.1	48	104.9	56.8	101.8	51.2	78.2	52.2
14	111.1	48.5	100.2	56.6	102.1	50.9	92.1	45.5
15	110.9	48.7	76.5	66.9	102	51.1	87.3	42.7