COMPARISON OF ON BOARD IMAGER [OBI] AND CONE BEAM COMPUTERISED TOMOGRAPHY [CBCT] FOR POSITION VERIFICATION IN PELVIC MALIGNANCIES ON IMAGE GATED INTENSITY MODULATED RADIOTHERAPY

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Certificate

This is to certify that the dissertation entitled "Comparison of On Board Imager and Cone Beam Computed Tomography for position verification in pelvic malignancies on image gated intensity modulated radiotherapy" is a bona fide record of the original work done by **Dr. Renitha Miriam Cherian** towards the partial fulfillment for the award of **Doctor of Medicine** in **Radiotherapy** of The Tamil Nadu, Dr. M.G.R Medical University, Chennai conducted in April 2014

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1. AIM OF THE STUDY

1. Comparison of On Board Imager [OBI] versus Cone Beam Computed Tomography [CBCT] in the verification of positional accuracy in pelvic malignancies in patients undergoing high precision Image gated intensity modulated radiotherapy [IG-IMRT]

2. Quantification and comparison of total, systematic and random errors in the mediolateral [x], craniocaudal [y] and antereoposterior [z] directions to help define the clinical target volume [CTV] to planning target volume [PTV].

3. To analyze the time trend in pelvic malignancies during Intensity Modulated Radio Therapy (IMRT) which may enable to reduce the number of Cone Beam Computed Tomography (CBCT) done in later weeks of radiotherapy.

INTRODUCTION

Radiation Therapy aims to deliver successfully the prescribed dose of radiation to the tumor while sparing the adjacent sensitive normal tissues.

As a result of the recent advances in the field of radiation oncology we have now entered the era of high precision radiation therapy such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT). These allow conformal treatment of tumor and conformal avoidance of normal tissues leading to improved tumor control and decrease in treatment-

Patient immobilization, tumor volume delineation, organ motion control and dose delivery verification are important factors in determining accurate delivery of treatment. These issues can decrease geographical miss and in turn provides increased local control and improves patient's outcome. The accuracy of the set up is the main concern to ensure delivery of the prescribed dose during treatment and to gain the desired tumor control probability (1).

However, many error sources exist from treatment preparation to execution that limits the accuracy of the treatment. As a result a safety margin is required to ensure that the planned dose is actually delivered to the target for all patients.

The important errors are Systematic Errors which occur during the initial set up and immobilization and persists until treatment delivery leading to a systematic organ motion error (1) and Random Errors are deviations between fractions, which are a result of day to

day variation in patient position and organ motion or otherwise called treatment execution errors(1).

Imaging prior to and during treatment plays a vital role in ensuring an accurate set up and in quantifying a safety margin to the clinical target volume to ensure that the target receives the actual dose (2).

This study aims to quantify and compare these errors using two modalities of imaging namely the Kilo Voltage Cone Beam Computed Tomography and the On Board Imager on patients who have a pelvic malignancy undergoing Intensity Modulated Radio Therapy, thus enabling to determine the required set up margins and positional accuracy during treatment.

2. LITERATURE REVIEW

2.1. HISTORY OF RADIOTHERAPY

Radiation Therapy field began shortly after the discovery of X-rays in 1895 by Wilhelm Rontgen. The following year, in 1896, Antoine-Henri Becquerel discovered the property which came to be known as Radioactivity. Building on the work of Becquerel, Pierre and Marie Curie discovered the radioactive elements Polonium and Radium (3).The field of radiation therapy grew quickly in the early 1900s largely due to the groundbreaking work of Nobel Prize-winning scientists Antoine-Henri Becquerel, Marie Curie and Pierre Curie.

Although promising as a therapeutic modality, the important limitation of the early X-ray machines to produce high energy, deeply penetrating beams was present. Therefore treatment of deep-seated tumors without excessive skin reactions was difficult(4).

In the 1960s, megavoltage treatment machines, known as Linear Accelerators were introduced which were capable of producing high energy, deeply penetrating beams, allowing treatment of deep seated tumors without excessive damage to the overlying skin and other normal tissues. In the 1970s and 1980s new imaging technologies, including magnetic resonance imaging (MRI) position emission tomography (PET) moved radiation therapy from 3-D conformal to intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT)(5).These advances have resulted in better visualization and targeting of the tumor resulting in better treatment outcomes, organ preservation and fewer side effects.

In 1993 the invention on the Multi Leaf Collimators [MLC] helped in delivering intensity modulated beams lead to the era of IMRT. These leaves were made up of tungsten alloy and each leaf width was equal to or less than a centimeter. These aided in delivering IMRT by a) multi-segmented static field delivery b) Dynamic delivery c) Intensity modulated arc therapy(6).

The multileaf collimator led to the era of Tomotherapy which used multileaf intensity modulating collimator [MIMiC]. This helped in treating the patient slice by slice as the couch moved continuously as in a helical CT scan(7).

2.2. HIGH PRECISION RADIOTHERAPY

Intensity modulated radiotherapy [IMRT] is a radiation treatment technique with multiple beams incident from different directions in which at least some of the beams are intensity modulated so that each beam intentionally delivers a non-uniform dose to the target (8).

It allows concave dose distributions and dose gradients with narrower margins than those possible using conventional methods thus avoiding close proximity organs at risk that may be dose limiting and provides increased tumor control through an escalated dose (9). In comparison with 3D conformal radiotherapy it has been proved to provide better dose distributions in some malignancies (10).

Image-guided radiation therapy represents a making of recent technological advances in medical imaging and conformal radiation therapy. The principle behind image-guided radiation therapy is acquisition of serial images using a variety of medical imaging techniques including computed tomography, ultrasound and magnetic resonance imaging. The current interests like positron-

emission tomography are additional functional imaging which augments these anatomic and volumetric image datasets. This ‘adaptive’ radiotherapy helps to recognize change in position of tumors and normal tissues during the course of treatment. As the position of the tumor and normal tissues change, the attenuation of radiation beams passing through these also change, causing an additional level of imprecision in targeting the tumor (11).

2.3. PROCESS AND THE STEPS IN IMRT

2.3.1. ***POSITIONING***: The position of the patient has to be maintained throughout the whole process of preparation, planning and treatment. This position will have to be comfortable as all these processes last for 15-30 min.

2.3.2. IMMOBILISATION

Reducing the patient movement and internal organ motion is critical for IMRT, as the dose distribution can be sculpted closer to the tumor volume and the organ at risk with rapid fall off outside the volume. Therefore it is very important that immobilization and reproducibility of patient are reconfirmed prior to the implementation of the treatment. The different immobilization devices used are alpha cradle, Vac-Loc system and pelvic board with aquaplast for pelvic tumors.

Patient marking, is usually done with permanent tattoos on the skin which allow easy positioning of the patient during treatment. Lasers are used during simulation and treatment to assist in patient positioning which also allow for accurate determination of the mechanical isocentre.

2.3.3. CT SIMULATION

Acquire a planning CT scan in the treatment position which is referred to as CT simulation. An important point to note is that the CT image set acquired with the patient in the treatment position on a flat couch which should be geometrically identical to the couch on which the patient will ultimately be treated.

2.3.4. TUMOUR DELINEATION

2.3.4.1. Image registration

The image registration is considered an important part of the IMRT process since it

a) aids in finding the transformation [translation, deformation and rotation] that maps one scan to another

b) helps in fusion of scans

c) used to align rigid structures.

Fusion of scans

This strategy combines physiological measurements or tissue characterization from nuclear medicine with the anatomic data from radiology or two radiological imaging.The fusion software calls for two sets of data for the one patient. One is selected as the "primary" to which the other would be registered. Since the two scans have been acquired at different times, in different machines and in different positions there would be a difference in slice thickness, pixel sizes and size acquisitions. The necessary adjustments are made for registration taking into account the x, y and the z coordinates.

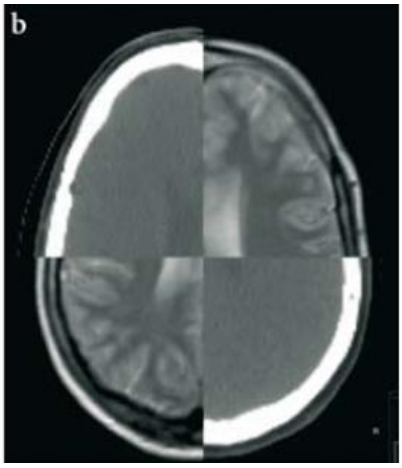


FIG 2-1: CT Fusion with MRI

Computed Tomography has played a key role in conformal radiotherapy. It has many advantages like high spatial resolution and spatial integrity, excellent bony structure depiction and also providing the relative electron density information for calculating the radiation dose. CT scans have also been used as a verification device during treatment execution.

Magnetic Resonance Imaging [MRI] has the advantage of providing excellent soft tissue discrimination which helps in better diagnosis and tumor delineation. It can be used in the clinical setting by using the fusion technique with CT for better tumor delineation. Fast cine MRI are also being made available which can help as an alternative for imaging the process of patient's breathing or cardiac rhythm. There have been also some developments like diffusion and perfusion MRI, Dynamic MRI, MR spectroscopy, MR angiography and functional MRI (5).

Positron Emission Tomography [PET] has been shown to be useful in studying the metabolic activity of tumors in vivo.Some initial studies have been reported where FDG-PET has been

incorporated into treatment planning and some recommendations have been formed(12,10). There have been pitfalls such as the FDG tracer being taken up non specifically by some benign conditions like brownfat, granulomatous diseases, pneumonia, inflammatory pathologies, muscle and bowel.The recent development of other tracers like flurothymidine [FLT] have been useful in increasing the sensitivity and specificity of PET(11).

New modalities like biological conformal radiotherapy [BCRT] are being introduced where the aim was to take in homogenous biological information which is derived from biological imaging into account and produce customized dose distribution which are non uniform on a patient specific basis(8).

2.3.4.2. Delineation of tumor and organs at risk

Tumor volumes are delineated on the CT scan meeting the requirements of ICRU 50 and 62. The gross tumor volume (GTV) is the gross palpable/ visible/demonstrable extent and location of the malignant growth. The GTV consists of primary tumor (GTV-T), metastatic lymphadenopathy (GTV-N), or other metastases (GTV-M).

The clinical target volume (CTV) is the tissue volume that contains a demonstrable GTV and is considered to contain microscopic, subclinical extensions of the tumor.

The ITV [Internal Target Volume} was defined as the CTV plus a margin taking into account the uncertainties in shape, size and the position of the CTV within the patient. Such a margin was called the Internal Margin (IM). For example, respiration, variable filling of the bladder and rectum and movements of the bowel(13).

A set-up margin (SM) is needed to account specifically for various uncertainties and variabilities in the reproducibility of patient positioning and inaccuracies in the alignment of the therapeutic beams during treatment planning and throughout treatment. The various factors like variations in positioning of patient , lack of reproducibility of the equipment (e.g. sagging of gantry, collimators, and couch) and human factors (e.g. experience of the radiotherapists and technologists).

The combined effect of an internal margin and a set-up margin to the CTV leads to planning target volume (PTV). The planning target volume (PTV) is a geometric concept, created to make sure the prescribed dose is delivered to the CTV.

Organs at risk (OAR) are normal tissues which are highly radiosensitive and could greatly influence the treatment planning.

An integrated margin which is added to the organ at risk to compensate for the variations and uncertainties is defined as the planning risk volume (PRV). The use of PRV has enabled IMRT planning with improved reduction of dose to critical structures(13).

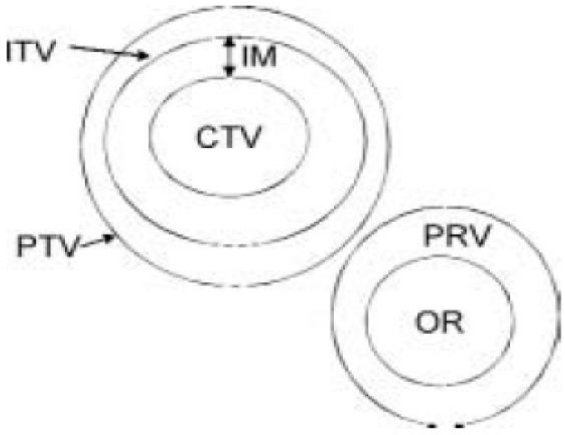


Fig 2.2.ICRU Volumes

2.4 PLANNING

2.4.1 Selection of treatment beams:

It is based on a combination of standard protocols, patient anatomy and experience of the planner. Selection of optimum beam directions has an effect on the required degree of intensity modulation within each field.

2.4.2. Dose prescription and constraints:

The prescription dose to the target and specified tolerance dose to the normal tissues are provided.

2.4.3. Plan optimization:

After the planner specifies the desired dose limits to the target and the normal organs at risk the computer optimizes the combination of dose intensity pattern of beams. The success of an optimization is based on the "cost function", which is the mathematical definition of the goodness of the treatment plan.

2.4.4. Plan Evaluation:

The plan is then evaluated based on planar dose distributions and dose volume histograms. If the dose distribution does not meet the clinical goals of treatment, the optimization parameters or the beams are adjusted and the process is repeated.

2.4.5. Quality Assurance:

The various factors of concern in an IMRT that need physics quality assurance will be the mechanical tests of the multileaf collimators, dosimetric measurements required for acceptance testing and commissioning and the tests specific to each individual patient's plan. Verification of the calculated monitor units and individual field intensity maps before treatment delivery is crucial.

Quantitative or quality individual field checks may be performed using film, EPID or diode arrays. Quantitative checks are done to ensure that the intensity map is correctly delivered. Printed isodoses can be used to compare the measured and predicted dose distributions (18).The gamma index an electronic format is used which examines how best the distributions agree with respect to dose difference and distance to agreement within the specified acceptance criteria (18,19). Since they were time consuming it led to the development of graphics based processing unit [GPU] based gamma index for fast calculations (20).

Qualitative checks are used to verify that the correct fields are being delivered or to monitor the reproducibility. A variety of phantoms can be used to verify the entire treatment delivery using different measuring devices like themoluminescent dosimeter, ion chambers and films. Monte Carlo codes for the entire treatment verification have been developed recently (21).

2.5. VERIFICATION OF PATIENT POSITION

Orthogonal images are used for verifying the isocenter in conformal radiotherapy. The reference images used can be either simulator images or digitally constructed radiographs. To perform accurate field matching, field sizes are chosen according to the appropriate anatomy (22).

2.6. TREATMENT DELIVERY

Intensity modulated radiotherapy is delivered with dynamic modulation using a multileaf collimator. This being computer based can be delivered as multisegmented static fields, dynamic fields or intensity modulated arc therapy (14).

2.7. MODALITIES OF POSITION VERIFICATION

In IMRT there are uncertainties exist in tumor target definition, immobilization of patient and physiological functions of the patient such as breathing, swallowing etc which make it difficult to administer high radiation to the planned target.

This led to the concept of Image guided intensity modulated radiotherapy which uses several methods for target localization like ultrasound, implanted fiducial markers, Megavoltage or Kilo voltage x-rays, optical tracking systems, in room CT scans [Kilo voltage CT on rail], Kilo

voltage or megavoltage cone beam CT and helical megavoltage CT which could be used to measure and correct errors that occurred prior or during the treatment delivery(20).

IG-IMRT plays an important role in eliminating or reducing the margins involved in defining the CTV and PTV(16, 17).

In the early days radiographic films were used for acquiring images for treatment verification which had its disadvantages that it required processing and also had a fixed dynamic range and digitization which made it impossible to use for online imaging and also required storage space. In the 1980's computed radiography came into light but had similar disadvantages as that of the films.

Electronic portal imaging devices [EPID] have been in the process of development for many years and was first introduced in the 1950's.The technology has developed over the years which could be broadly classified as camera based systems, ionization matrix devices, scanning array and other systems like flat panel devices and amorphous silicon devices. Obtaining rapid high quality images and flexibility in computer digitization helps in online corrections and thereby reduces set up errors. The x-ray image transducer panels using Selenium and amorphous Silicon [aSi] was an improvement in the EPID technology despite its disadvantages of employing megavoltage imaging. However these flat panel inducers provided the basis for the practical implementation of imaging with Kilo voltage x-rays which is being developed as the imaging technology of the new era in conformal radiotherapy(23,24).

2.7.1. KILOVOTAGE IMAGING

The use of Kilo voltage [KV] x-ray imaging for set up verification is historical. In the 1950s the cobalt-60 unit had a separate KV x-ray system attached to it. By the mid 1980s Biggs et al, (23) introduced the KV source mounted on a medical accelerator Shiu et al in 1987(24) introduced the set up verification by using cobalt -60 treatment beams with a KV gantry mounted source on the film to yield better quality images. Cho and Munroe in 2002 (25) introduced the design of the new x-ray target which produced both KV and megavoltage [MV] beams. Akoi et al (25) developed the integration of a CT scanner with a medical accelerator in the treatment room with a communal couch and software utilities. In 1995 Jaffray et al (11) described an imaging system which was dual beam consisting of KV and MV imaging systems. There was a KV source mounted at 45 degrees from the MV source and a shared CCD imaging device. This system rapidly evolved and was also capable of tomographic imaging using cone beam CT scan. In 1999 Jaffray, Drake et al (11) developed it into a device with dual sources mounted 90 degrees apart and dedicated CCD imaging device for each source. This eventually led to the development of the "synergy" accelerator by Elekta Inc which was also available in other commercially similar "On Board imager" KV imaging systems by Varian medical systems.

In room KV systems can be broadly classified on the basis of installation as

- Rail track –mounted system
- Ceiling/floor- mounted system
- Gantry-mounted system.

ON BOARD IMAGER AND CONE BEAM COMPUTED TOMOGRAPHY

2.7.1.1. ON BOARD IMAGER

This KV imaging system consists of 3 robotic arms. The EXaCT arms, the two electronically stabilized arms that hold x–ray tubes [G242] and the high performance flat panel imagers and the third identical robotic arm which holds the MV imager. The position of the imager of the OBI is set at 50cm below isocenter. It can be moved +0.5cm above isocenter to -80cm from the isocenter along the direction of the KV beam. Depending upon the source to imager distance it can be moved laterally by +/-16cm and extended 19.5 to 23cm past the isocenter. The x-ray tube can be positioned at either 80cm or 100cm from the isocenter.

The EXaCT arms position can be parked, partially extended and in the extended position and can be controlled remotely. The arms can be controlled either individually, as a pair [OBI source and imager] or as a triple [OBI plus MV imager].

- <u>32kW X-Ray Generator:</u>
- Mounted in Gantry Stand (Right Hand Sid)
- 40 – 150 KV range
- 10 – 320 mA

- G242 X-ray tube:
- [**KVS**] Arm mounted at 270° position
- 0.4 & 0.8mm focal spot sizes
- 14 degree anode angle
- KV Imager
- PaxScan 4030CB a-Si panel
- [**KVD**] Arm mounted at 90° position
- ~ 40 x 30cm (landscape)

The KV X –Ray source is located between 80 and 100cm from the isocenter of the machine and the KV source collimator is used for asymmetrical and symmetrical fields with the blade position.

MV Imager

- Portal Vision a-Si 1000 panel
- Image Acquisition System [**IAS**]
- 1024 x 768 pixels at full resolution.

The On Board imager is capable of the radiographic and the fluoroscopic mode.

Fluoroscopy:

It produces pulsed images ms at 15fps.It is taken at a tube voltage range of 40 to 125KV range and upto 80mA tube current.

The uses of fluoroscopy are for pre treatment motion assessment, setup of gating and tracking parameters and for intra fraction respiratory tracking and compensation.

Digital Radiography:

It is used for general kilo voltage imaging rather than fluoroscopy. It is taken at a tube voltage of 40-150KV range and a tube current of upto 320mA. The panel pixels read out at high and low sensitivities depending on the dual or single gain effect and the system selects which results provide more information based on the saturation levels, namely increase in the dynamic range, and increase in contrast between bone and soft tissue. The standard resolution for dual gain is 1024x768 pixels and the high resolution for a single gain effect is 2048x1536 pixels.

ADVANTAGES

- The orthogonal portal images both MV and KV can be acquired without gantry rotation for antereoposterior and lateral online set up or for the KV/KV image pair.

- The couch position and angle can also be corrected based on 2D matching between portal images and the digital radiograph images.

The advantages of the kilo voltage imaging compared to the megavoltage imaging is that

- There is better bone and soft tissue contrast
- Lesser radiation dose

- No metal artefacts
- Fluoroscopic imaging
- It is not the treatment beam
- It is not real time imaging

RADIATION DOSE OF KILO VOLTAGE PORTAL IMAGING

The dose to the rectum from a kilo voltage source was approximately 99% lesser for two portal images than that made with megavoltage source a 5MU/exposure. The dose at skin was 98% lower from a kilo voltage source(26).

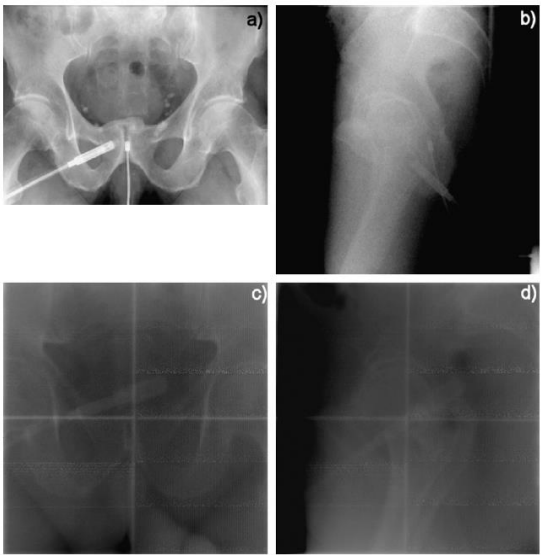


Figure: 2.2 a & b: KV imaging at 0 and 90 degrees respectively

Figure: 2.3 c & d: MV imaging at 0 and 90 degrees respectively

2.7.1.2. CONE BEAM COMPUTED TOMOGRAPHY

Kilo voltage cone-beam computerized tomography (KV- CBCT) systems integrated into the gantry of linear accelerators are used to acquire high-resolution volumetric images of the patient in the treatment position. Using on-line software and hardware, the position of the patient can be determined accurately with a high degree of precision and the set-up parameters can be adjusted to deliver the accurate treatment.

The capabilities of CBCT include

- 600 to 750 projections
- 370 degree gantry rotation
- Acquisition time of 65seconds
- Approximately 2.5minutes totally for acquisition and reconstruction of images
- Has a beam angle of 14 degrees

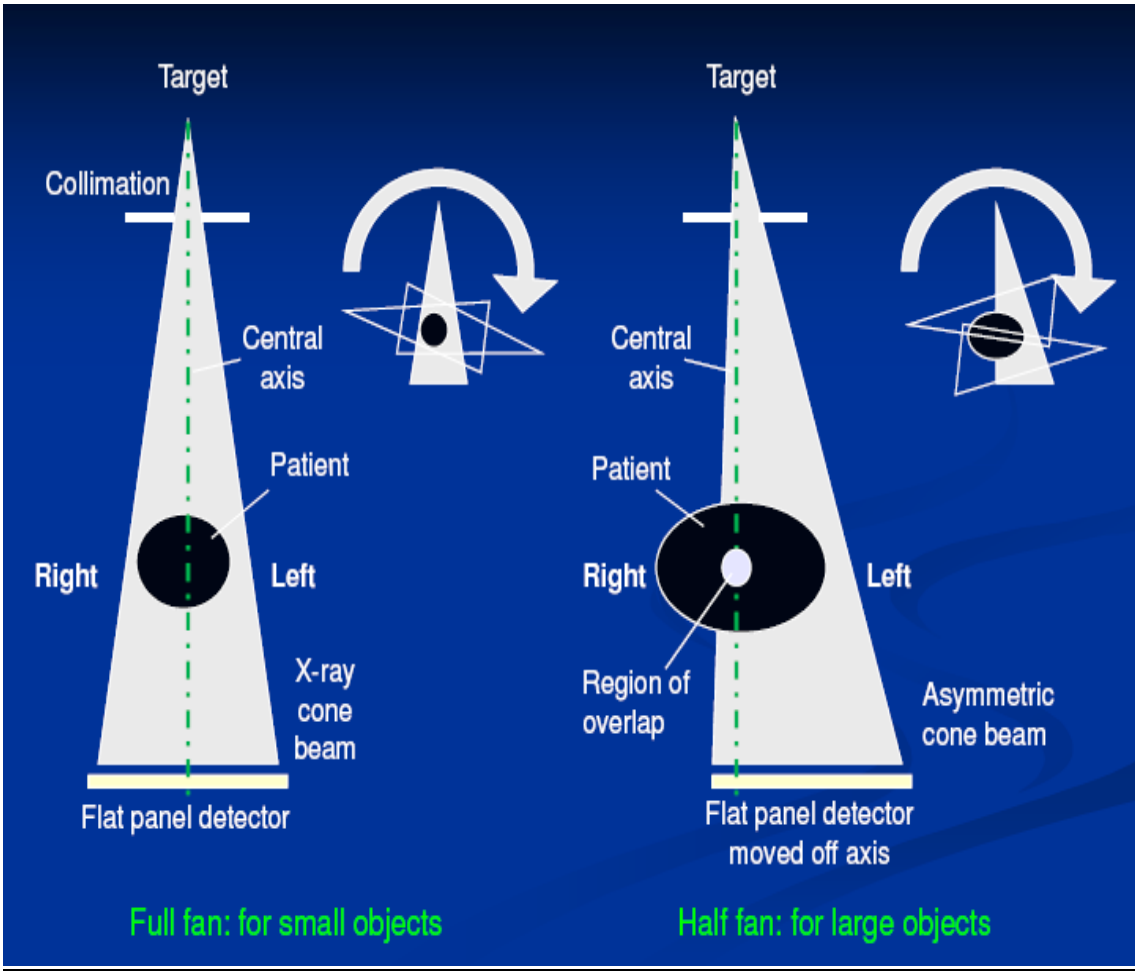
MODES OF CBCT ACQUISITION

FULL FAN DETECTOR

- Detector centered 30 x40
- Reconstructed field of view at 24cm in diameter
- 15cm in Craniocaudal [C-C] extent
- Full bow tie used
- Used for smaller sites

HALF FAN DETECTOR

- Detector shifted by 14.8cm
- Field of view 45cm in diameter
- 14cm C-C extent
- Half bow tie used
- Used for larger sites



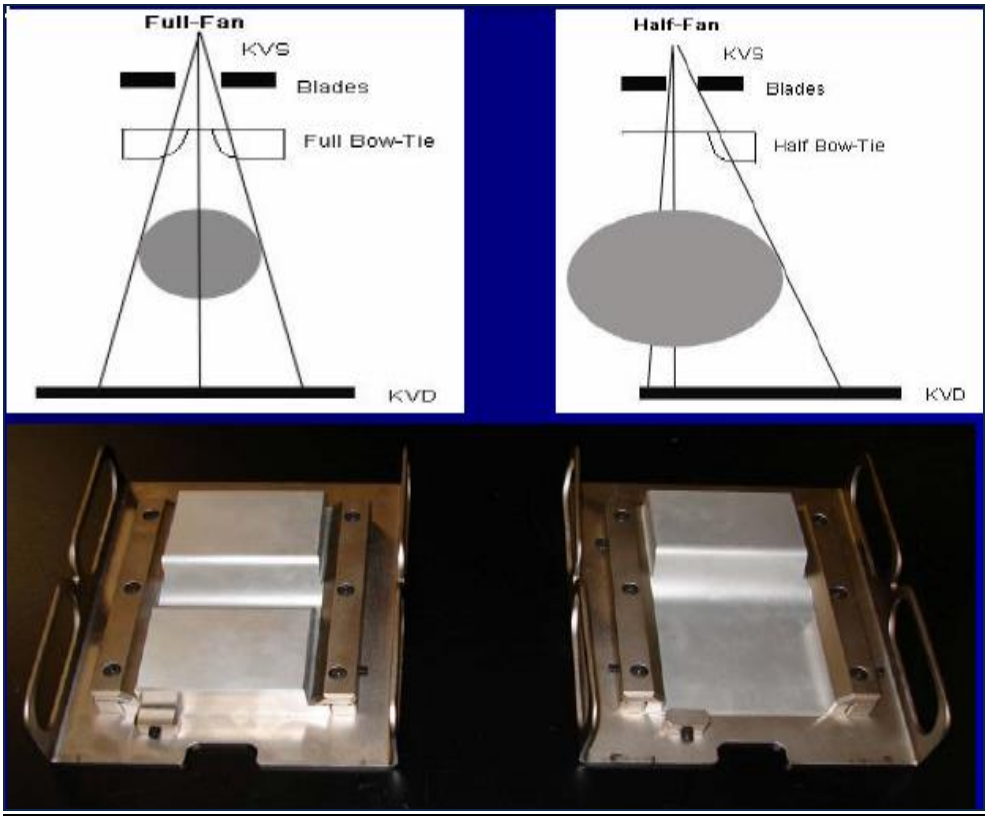


Figure: 2.4: CBCT FANS

RADIATION DOSE IN CBCT

Various studies(27) have been done on studying the radiation dose delivered by the kilo voltage cone beam computed tomography. There are various factors that influence the radiation dose delivered during cone beam CT. Patient related factors like patient size and technical factors like kilo voltage, number of frames to reconstruct an image, milli Amperes and time per frame (ms) and field size.

A study on doses of CBCT in prostate cancer(28) showed that the measured antero posterior skin dose was lesser for a larger patient but it did not influence the lateral doses much. The left lateral doses were approximately 40% higher than the right lateral dose which was justified since the

KV source rotation started from the left lateral side of the patient and ended on the same side and in the 370 degree scan rotation there can be an overlap of 10 degree on the left lateral side.

In a study done by Dufek et al(29), measurement of organ doses by means of themoluminescent dosimeter were performed in a male anthropomorphic Rando phantom from one CBCT scan, two MV images and two KV images of pelvis which were 1-6, 1-10 and 0.05-1 %, respectively, of the organ doses resulting from one fraction of prostate radiotherapy. The maximum effective doses from CBCT scans, KV images and MV images of pelvis were 5.6, 0.8 and 11.9 mSv, respectively.

Study done by Ding et al(30), also showed that the doses of CBCT can be minimized by reducing the scan length, the exposure settings, selection of the gantry rotation angles, and also by using the full fan bow-tie in the needed situations.

BASIC APPROACH OF THE OBI AND CBCT

- To create set up fields and reference images [2D] in database
- To define the anatomical structures or markers
- To set up the patient on the couch
- Acquire 2D/3D image with OBI/CBCT
- Analyse and match images-determine the shifts
- Apply the corrective shifts
- Treatment delivery

2.8. ERRORS

DEFINITION:

Error is defined as the difference between the actual and intended position of the part of the patient that is irradiated, with respect to the treatment beam(s) during treatment.

2.8.1. SOURCES OF ERRORS

According to the ICRU there are three sources of geometrical uncertainty which may interfere with the accurate delivery of a treatment plan namely,

(1) variation in the patient set up like daily positioning of the patient on the couch,
(2) variations due to organ motion and deformation like bladder or rectum filling variati
(3) due to machine related errors like beam sizes or gantry which contribute a small part compared to the other two causes (27).

2.8.2. QUANTIFICATION OF SET UP ERRORS

2.8.2.1. SYSTEMATIC ERRORS

Systematic Error is the deviation between the planned patient position and average patient position over a course of fractionated therapy which is caused due to errors during treatment planning. They can be errors in the position of patient during planning CT or errors during target delineation. These are called treatment preparation errors.

2.8.2.2. RANDOM OR INTERFRACTION ERRORS

Random errors are deviations between different fractions, during a treatment series which are a result of day to day variation in patient position and organ motion or otherwise called treatment execution errors.

2.8.3 EFFECT OF ERRORS ON DOSE DISTRIBUTION

Systematic and Random Errors have different effects on the dose distributions.

Systematic Errors cause a shift in the cumulative dose distribution relative to the target which leads to serious consequences like the CTV shifts out of the high dose region. This can affect all fractions (28)

Random Errors lead to blurring of the dose distribution. They will point in varied directions for different fractions which result in a much smaller dose effect as compared to systematic errors. This blurring effect causes a small decrease in the dose at the edge of the high dose region which can affect the treatment.

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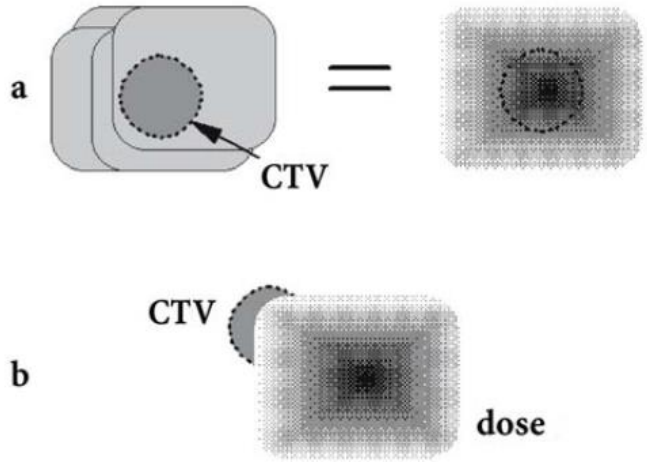

Figure: 2.5: Systematic and Random Errors

Systematic errors lead to a shift of cumulative dose distribution relative to CTV & Random errors lead to blurring of dose distribution

2.8.4. CALCULATION OF SYSTEMATIC AND RANDOM ERRORS:

The errors [translational] are measured in 3 directions namely cranial-caudal[CC], anterior-posterior [AP] and the mediolateral axis [ML]. Cranial-caudal axis is measured from head to the feet, mediolateral axis from the left to the right side and the anterior-posterior axis from the backside to the front side. Systematic and Random Errors are calculated in each direction separately and then mathematically combined to obtain a 3D displacement vector.

2.8.5. TIME TRENDS:

It is defined as the consistent gradual drift in the set up errors during the complete course of treatment. Researchers like El Gayed et al(33), 1993 reported significant time trends in set up errors in 5 out of 20 patients. Osei et al in 2009(34) studied online correction of set up errors and displacement in prostate cancer using gold seeds and imaging with EPID and DRR and concluded that there were no significant time trends observed during the course of treatment. In a study done on pre-treatment position verification of patients with prostate cancer on high precision radiotherapy comparing KV images and CBCT, they were statistically significant changes in the time trend for 4 patients among KV results and 3 patients in the CBCT results(29).

2.9. DETERMINATION OF SAFE PTV MARGIN

To accommodate inter and intrafraction set up errors in patients, the ICRU recommended expanding the clinical target volume (CTV) by a margin to obtain the planning target volume (PTV).

Several authors have conducted studies on obtaining the correct CTV to PTV margin both for the target as well as for the organs at risk like Stroom et al, (31), Mc Kenzie et al(36).

The Van Herk model formula [VHMF] assumed both Systematic and Random Errors to be normally distributed and the standard deviations (SDs) of Systematic and Random Errors, assumed common to all axes, were denoted by Σ and σ. The required margin was given as: $M = 2.5\Sigma+0.7\sigma$. This formula ensured that 90% of patients experience a CTV minimum dose (after

setup errors) which is greater than or equal to the planned PTV minimum. The VHMF was based on several assumptions like

(a) Homogeneous tissue

(b) A number of fractions that is sufficiently large for the sum of fraction doses to be well-approximated by a convolution (convolution method)

(c) A spherical target that is large compared to the setup errors,

(d) A normal beam penumbra of width ~0.5 cm and

(e) An isodoses surface exactly conforms to the PTV, so that any movement of the CTV outside the PTV reduces the minimum CTV dose below the planned minimum PTV dose. Studies by Gordon et al and Craig et al on prostate, lung and breast malignancies showed that tissue in homogeneities have little effect on margins.

Finite fraction issues were addressed by Van Herk et al(32). Gordon and Siebers(37)and others like Craig et al (37) found out that VHMF was inaccurate for sigma more than 0.2 because it failed to account for non negligible variability in the dose which were associated with Random Errors. When sigma is lesser than egual sigma (P) which is 0.32, variability in dose due to random errors becomes negligible, and the convoluted method and VHMF becomes valid regardless of the values of sigma and number of fractions [N]. When sigma is greater than or approximately egual sigma (P), it was found that the VHMF can underestimate margins for large and small sigma and small n. As a consequence of this underestimate, the CTV minimum dose can fall below its planned value in more than the prescribed 10% of treatments. So alternative algorithms like were developed since they concluded that the VHMF which is based on the

convolution method should be used with caution in hypo fractionated or adaptive therapy regimens.

Dosimetric margin distribution [DMD] is a new concept for calculating the margins which is being evaluated by authors. It is defined as the margin distribution achieved between the CTV and the treatment volume [TV]. The sensitivity of the CTV dose to errors in the set up is a function of the TV and not the PTV. VHMF identifies TV with the PTV by assuming tight conformance of the dose to the PTV, but TV is larger than the PTV which resulted in the disagreement between the theory and application of VHMF which led to this concept.

Dosimetric margins extend beyond the CTV-to-PTV margin which results in it overcompensating for set up errors and thus achieving a level of target coverage that is higher than the specified value. Thus the resulting plans will be able to tolerate larger setup errors.

The dosimetric margin distribution could have the potential to be a useful tool in assessing the effects of setup errors on treatment plans and also in modifying the plans so that they are more strong with respect to errors(30).

3. MATERIALS AND METHODS

3.1. STUDY DESIGN

This is a descriptive study comparing the On Board Imager [OBI] versus Cone Beam Computed Tomography [CBCT] in the verification of positional accuracy in patients undergoing high precision Image Gated Intensity Modulated Radio Therapy [IG-IMRT] for pelvic malignancies. Quantification and comparison of total, systematic and random errors in the mediolateral [x], craniocaudal [y] and antereoposterior [z] directions were done which in turn help in defining the clinical target volume [CTV] to planning target volume [PTV].

3.2. SAMPLE SIZE

All the patients who had been diagnosed to have a pelvic malignancy and on IG-IMRT from January 2012 to August 2013 were included in the study since it was a descriptive study.

3.3. INCLUSION CRITERIA

Patients with a pelvic malignancy who were undergoing intensity modulated radiotherapy and those who consented for the study were included.

3.4. STUDY PROTOCOL

The protocol described below was used for patients who consented to participate in the study

3.4.1. PRE REQUISITE:

The study was reviewed and cleared by the Ethics and Research Committee of the Institutional Review Board. The patients were explained the details of the study and were given a written description of the study. Once they consented and signed the informed consent form, they were included in the study.

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3.4.2. IMMOBILISATION DEVICE:

The immobilization device used was Vac-loc or a vacuum bag shaped to the individual's body contour which prevented the movement of the patient during planning and treatment.

3.4.3. SIMULATION AND IMAGING:

After immobilization the patient was simulated in a VARIAN simulator. Three reference points were marked on the patient's body in the treatment field using lasers and were tattooed. A CT scan was acquired with 5mm cuts in supine position. Radio opaque markers were placed on the 3 centers which made it visible in the CT images. Contrast agents are used both orally and intravenously for enhancing the quality of the images and for better delineation of lymph nodes and bowel.

3.4.4. VOLUME DELINEATION:

The CT images were registered and transferred to the ECLIPSE planning system(version 1.5) The Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV), Organs at Risk (OAR) and Planning Risk Volume of OAR's (PRV) were delineated in each slice of the CT scan according to ICRU 50 and 62 guidelines. A margin of 5mm was given to the CTV to obtain the PTV.Dose constraints were provided for the organs at risk.

3.4.5. PLANNING:

The planning was done on the ECLIPSE treatment planning system version 10.1.

DRR's were generated for all the treatment fields and 2 orthogonal images were generated [AP and Lateral] for the purpose of treatment verification. Then once the plan was finalized, the scheduling of the treatment, assignment of dose limits and rearranging the treatment fields was done. Then the images were sent to the treatment unit via ARIA.A quality assurance on the plan was done before the initiation of the treatment.

3.4.6. TREATMENT UNIT

The treatment used for treating the patients was the Varian CLINAC 2100-C/D.It is dual energy treatment unit with 6MV and 15MV and electron energies 4MeV, 6MeV, 9MeV, 12MeV and 15MeV. It has the facilities for IMRT and IGRT. The maximum field size is 40x40cm. It has 60 pairs of multi leaf collimators which are made up of tungsten. The 40 pairs in the middle have a leaf diameter of 0.5cm and the 20 pairs of leaves on either side have a leaf diameter of 1cm. It has the on board imager software which is used for treatment verification.

The 2D-2D matching systems available are the

a) kV-kV b) kV-MV c)MV-MV using the On Board Imager.

The 3D-3D matching system is done using the Cone Beam Computed tomography. The CBCT scan consists of a full beam and a half beam CT. In pelvic malignancies the full tie bow filter is used in the CBCT.

3.4.7. TREATMENT VERIFICATION

The treatment verification were done on days 1, 2 and 3 and weekly once for the entire duration of treatment. The verification was done with an On Board Imager by obtaining antereoposterior and lateral images and CT images on a Cone Beam CT scan.

The analysis of the images was done online and displacements beyond the tolerance limits were corrected.

3.4.8. IMAGE ANALYSIS

Analysis of the images was done after image registration. After mutual intensity based registration by OBI the DRR was fused with the OBI image and the CBCT image respectively. The 2D-2D matching was done with the help of the virtual cross hairs. The 3D-3D matching was done with a) automated gray scale value matching and b) manual matching.

First the 3D matching was done with the automated matching where only a global matching will be possible and it is then matched manually according to the anatomy.
The shifts in all 3 directions were noted and the displacements beyond the tolerance limits were shifted accordingly.

3.5. STATISTICAL ANALYSIS

3.5.1. ERRORS

The total errors in the three directions [mediolateral, craniocaudal and antereoposterior] were measured. Displacements obtained each day were compiled and the following were calculated.
The Systematic Error [SE] is arrived at by summing up the measured set up error for each imaged fraction [$\Delta_1+\Delta_2+\Delta_3$] and then dividing that by the number of fractions[n]. The Systematic Error was calculated for the first 3 days and the patient was shifted accordingly and treated.

$M = [\Delta_1+\Delta_2+\Delta_3] /n$

The overall population mean set up error [M_{pop}] is the means of each individual patient (individual systematic error m_1, m2, m3 in x, y and z directions) being summed and the total divided by the number of patients in the analysed group[p].

$M_{pop} = m_1+m_2+m_3 / p$

The Population Systematic Error [Σ^2] is the Standard Deviation of the distribution of the mean errors for each individual patient. It is arrived at by summing the squares of the overall population mean and the resultant sum is divided by the number of patients and the square root of the resultant value is taken.

$\Sigma^2 = \sqrt{(m_1 - M_{pop})^2 + (m_2 - M_{pop})^2 + (m_3 - M_{pop})^2 / p}$

Random Error [σ] is the Standard Deviation of all the measured errors over the course of treatment. It is calculated by summing the squares of set up error from each image in inturn. The resultant sum is divided by the number of images and the square root of the resultant value gives the individual Random Error.

The Random Error was calculated from the first week of treatment till the end of treatment.

$\sigma^2 = \Delta_1^2 + \Delta_2^2 + \Delta_3^2 / n-1$

Population Random Error [σ^2] is the mean of the individual random errors which is taken as the mean of all the individual random errors.

$\sigma = \Delta_1+\Delta_2+\Delta_3+\Delta_{4\ldots\ldots} / p$

The Systematic and the random errors in the mediolateral, craniocaudal and the antereoposterior directions measured by the OBI and the CBCT were compared by the Bland Altman plots and a paired sample nonparametric test , wilcoxon signed rank test was done to acquire a P value to ascertain its significance.

A P value ≤ 0.05 was considered to be significant in the statistical analysis.

3.5.2. 3D VECTOR DISPLACEMENTS OR ERRORS

The 3 dimensional vector was calculated for the Systematic and the Random components from the displacements measured in each direction. It indicates the magnitude of displacement in any spatial direction from the reference position. It is calculated using the formula

$D_{3D} = \sqrt{(d^2_{ap} + d^2_{cc} + d^2_{ml})}$ where the d_{ap} ,$d_{cc,}$ d_{ml} are the displacements in the antereoposterior, craniocaudal and the mediolateral directions respectively.

3.5.3. CTV TO PTV MARGIN CALCULATION

The CTV to PTV margins were calculated using three formulas as suggested in literature.

1. ICRU 62: (Population systematic error [Σ] +0.7 x population random error [σ])

2. Stroom's formula: (2 x population systematic error + 0.7 x population random error)

3. Van Herk's Formula: (2.5 x population systematic error + 0.7 x population random Error)

Comparison between the two modalities of set up verification [OBI and CBCT] was done using the Stroom's formula.

A Bland-Altman plot was done to compare the two modalities and the non parametric wilcoxon signed rank test was done to ascertain the significance.

A p value ≤ 0.05 was considered to be significant statistically.

3.5.4. TIME TREND ANALYSIS

The average total error obtained for all the patients in the mediolateral, craniocaudal and antereoposterior directions on the first 3 days and weekly once were plotted against time to see the impact of time on displacement for both modalities.

4. RESULTS

All the patients with a pelvic malignancy on IG-IMRT from January 2012 to August 2013 and signed the informed consent were enrolled in the study. A total number of 15 patients were enrolled in the study.

During the treatment, each patient had an OBI and CBCT taken on the first 3 days of treatment [days 1, 2 and 3] followed by weekly once. The displacements in the antereoposterior, mediolateral and the craniocaudal directions were computed and the errors more than the tolerance limit [5mm] were shifted and corrected. The Systematic, Random and Radial Errors were calculated for both the OBI and the CBCT.

4.1 PATIENT CHARACTERISTICS

Sex	**Number of Patients**
Male	5
Female	10

Table 4.1.1: Sex distribution

Diagnosis	**Number of Patients**
Carcinoma Prostate	2
Carcinoma Cervix	6
Carcinoma Vagina	1
Carcinoma Endometrium	1
Carcinoma Rectum	5

Table 4.1.2: Diagnosis

Number of Patients	Energy of beam	Dose in cGy	Number of Fractions
1	6MV	4500	25
2	6/15MV	5000	25
10	6MV	5040	28
2	6MV	7640	41

Table 4.1.3: Treatment Characteristics

Table 4.1.1 shows that 5 males and 10 females were included in the study and Table 4.1.2 shows that the maximum number of patients had gynecological malignancy(8/15), 2 patients had carcinoma prostate and 5 had carcinoma rectum. Table 4.1.3 depicts the energy used, dose and fractionation of treatment delivered for each patient.

4.2 ERRORS

The two main types of errors are the systematic error and the random errors. The mediolateral shift (x), craniocaudal shift (y) and the antereoposterior shift (z) were measured for all patients in OBI and CBCT. The radial error or the length of the mean vector displacement was also calculated using the Euclidean distance formula for the 3 dimensions x, y and z. The systematic and random errors were calculated based on these measured shifts.

4.2.1 CONE BEAM COMPUTED TOMOGRAPHY

4.2.1.1: SYSTEMATIC ERRORS

Definition: This is the deviation between the planned patient position and average patient position over a course of fractionated therapy which is caused due to errors during treatment planning.

Patient No.	x (cm)	y(cm)	z(cm)	Radial Error
1	0.40	0.30	0.73	0.89
2	0.13	0.27	0.27	0.40
3	0.10	0.37	0.23	0.45
4	0.17	0.07	0.03	0.18
5	0.37	0.17	0.93	1.02
6	0.30	0.20	0.17	0.40
7	0.20	0.20	1.80	1.82
8	0.33	0.33	0.57	0.74
9	0.60	0.20	0.20	0.66
10	0.37	0.40	0.50	0.74
11	0.20	0.07	0.33	0.39
12	0.17	0.10	0.23	0.30
13	0.17	0.03	0.10	0.20
14	0.53	0.90	0.90	1.38
15	0.37	0.43	0.43	0.71
Mean	0.2933	0.2689	0.4956	0.6853
SD	0.14864	0.21509	0.45545	0.45318
Minimum	0.10	0.03	0.03	0.18
Maximum	0.60	0.90	1.80	1.82
Percentile	Quantiles			
25^{th}	0.1667	0.1000	0.2000	0.3944
50^{th}[median]	0.3000	0.2000	0.3333	0.6633
75^{th}	0.3667	0.3667	0.7333	0.8876

Table 4.2.1.1: Systematic Errors in cm in the x, y and z direction and radial errors using CBCT

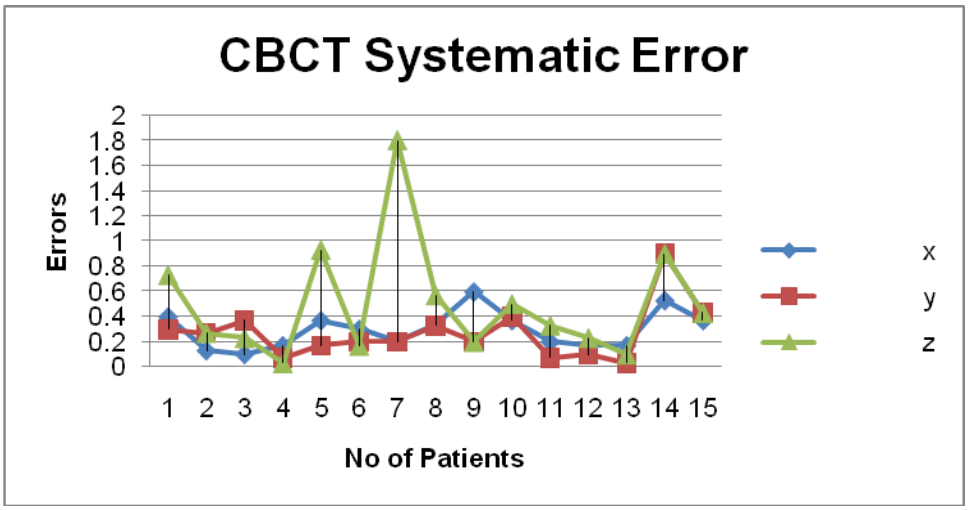

Figure: 4. 1: Systematic Errors measured by CBCT in cm in the x, y and z directions for the 15 patients

The systematic errors of the CBCT ranged from 0.10 to 0.60cm in the x direction, 0.03 to 0.90cm in the y direction and 0.03 to 1.80cm in the z direction respectively. The shift exceeded the tolerance in 2 patients in x direction, 1 patient in the y direction and 6 patients in z direction. One patient had significant shift in all the three directions. The median shift was within the tolerance and 75^{th} percentile exceeded the tolerance only in z direction.

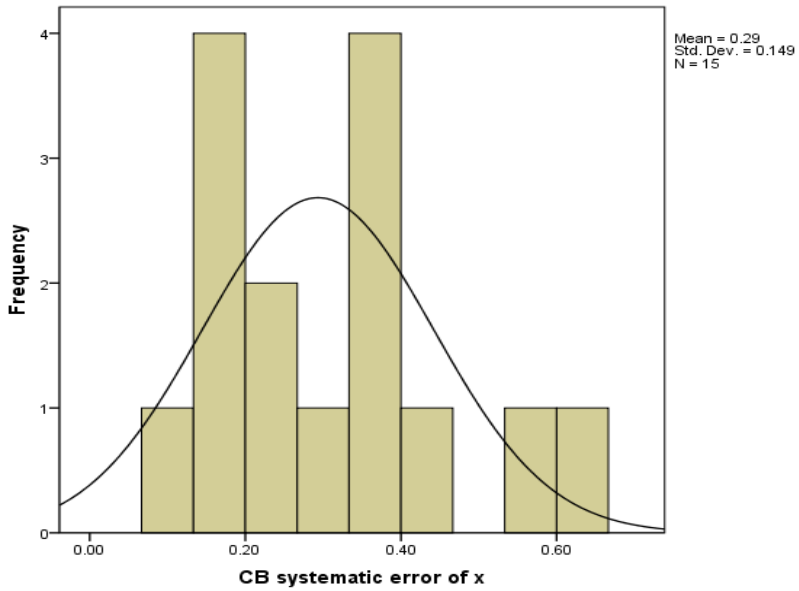

Figure: 4. 2: Systematic Errors measured by CBCT in the x direction in cm

Figure 4.2 shows the histogram of the systematic errors of CBCT in the mediolateral direction and the graph shows that most of the errors were within 0.5cm. Two patients had an error of more than 0.5cm (0.53 and 0.6cm).

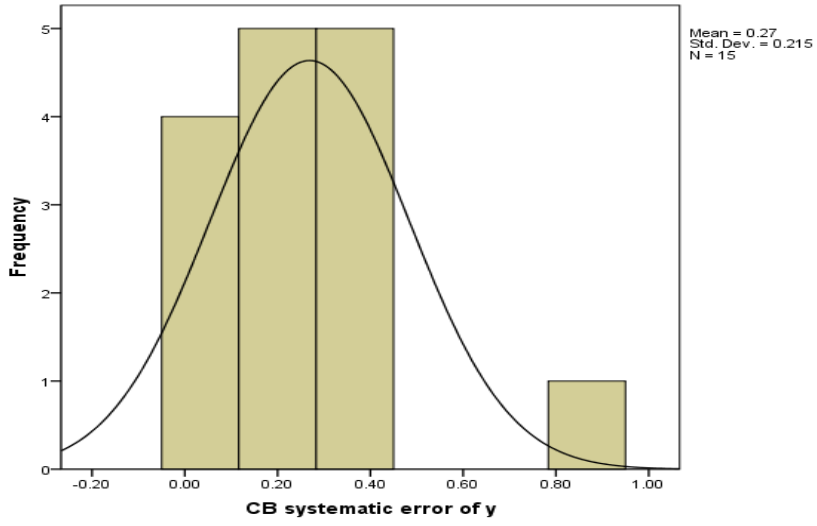

Figure: 4. 3: Systematic Errors measured by CBCT in the y direction in cm

Figure 4.3 shows the histogram of the systematic errors in CBCT in craniocaudal direction and the graph shows that most of the errors were within 0.5cm. Only one patient exceeded the tolerance and had an error of 0.9cm.

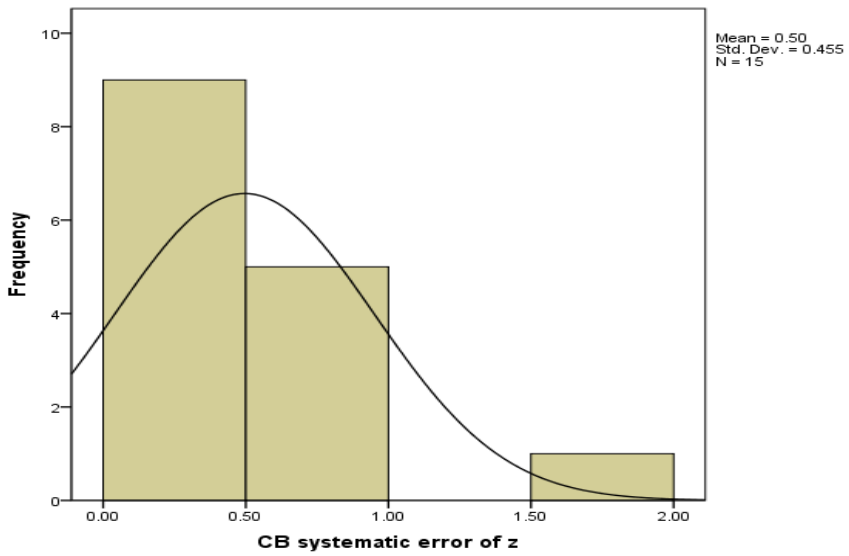

Figure: 4. 4: Systematic Errors measured by CBCT in the z direction in cm

Figure 4.4 shows a histogram of the systematic errors of CBCT in antereoposterior direction and the graph shows that 9 patients had errors within 0.5cm, 5 were ranging from 0.5 to 1cm and 1 patient had an error of 1.80.

4.2.1.2 POPULATION SYSTEMATIC ERROR CBCT

Systematic Error	No of Patients	Overall Population Mean Set Up Error [Mpop]	Population Systematic Error ∑2
x	15	0.29	0.02
y	15	0.26	0.04
z	15	0.49	0.22

Table 4.2.1.2: Overall Population Mean Setup Error and the Population Systematic Error using CBCT: The Population systematic errors were 0.023673, 0.049569 and 0.22225623 cm in the x, y and z direction respectively as shown in Table 4.2.1.2.

4.2.2 ON BOARD IMAGER

4.2.2.1 SYSTEMATIC ERRORS

Patient No.	x [cm]	y[cm]	z[cm]	Radial Error
1	0.43	0.13	0.63	0.78
2	0.13	0.40	0.17	0.45
3	0.10	0.43	0.10	0.46
4	0.07	0.07	0.03	0.10
5	0.07	0.13	0.03	0.15
6	0.00	0.00	0.00	0.00
7	0.16	0.10	1.30	1.31
8	0.03	0.23	0.23	0.33
9	0.50	0.10	0.07	0.51
10	0.03	0.67	0.37	0.76
11	0.13	0.03	0.20	0.24
12	0.37	0.23	0.60	0.74
13	0.13	0.23	0.30	0.40
14	0.43	1.10	0.27	1.21
15	0.70	0.50	0.23	0.89
Mean	0.2200	0.2844	0.3022	0.5566
SD	0.2115	0.21509	0.45545	0.45318
Minimum	0.00	0.00	0.00	0.00
Maximum	0.70	1.10	1.30	1.32
Percentile	Quantiles			
25^{th}	0.0667	0.0667	0.0667	0.2427
50^{th}[median]	0.1333	0.2333	0.2333	0.4558
75^{th}	0.4333	0.4333	0.4333	0.7789

Table 4.2.2.1: Systematic Errors in cm in the x, y and z directions and radial errors using the On Board Imager.

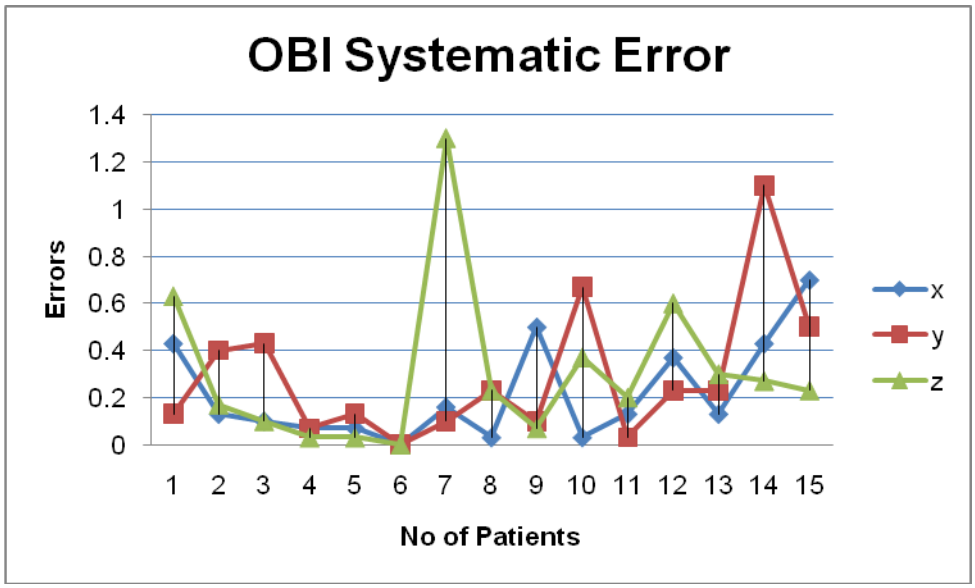

Figure: 4. 5: Systematic Errors measured by OBI in cm in the x, y and z directions for all 15 patients

The systematic errors of the OBI ranged from 0.0 to 0.7cm in the x direction, 0.0 to 1.10cm in the y direction and 0.0 to 1.30cm in the z direction respectively as shown in Table 4.2.2.1. The shift exceeded the tolerance in 1 patient in x direction, 2 patients in y direction and 3 patients in z direction. The median shift and shift in 75th percentile were within the tolerance in all three directions.

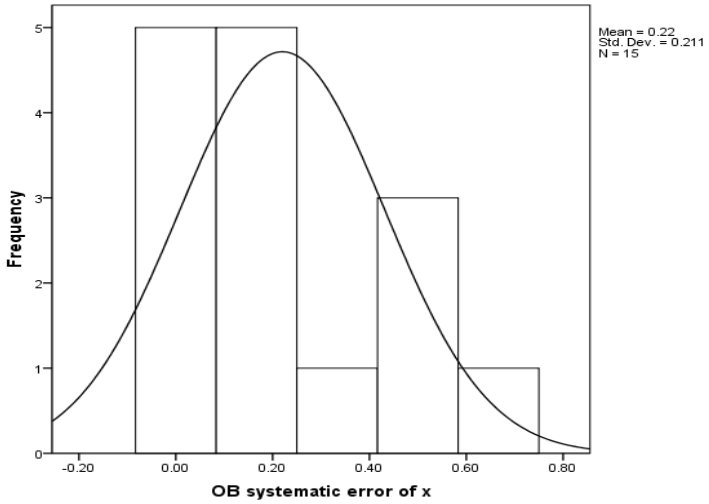

Figure: 4. 6: Systematic errors measured by OBI in the x direction in cm

The Figure 4.6 shows the histogram of the systematic errors of OBI in the mediolateral direction and the graph shows that most of the errors were within 0.5cm. Only one patient had an error of 0.70m

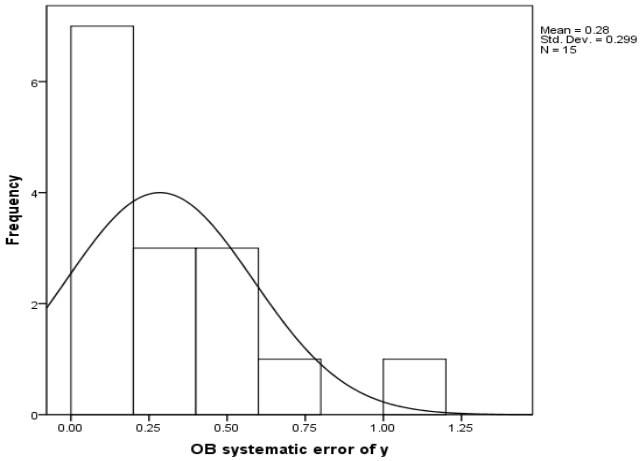

Figure: 4. 7: Systematic errors measured by OBI in the y direction in cm.

Figure 4.7 shows the histogram of the systematic errors of OBI in the craniocaudal direction and the graph shows that most of the errors were within 0.5cm and two patients who had errors of 0.67 and 1.10cm.

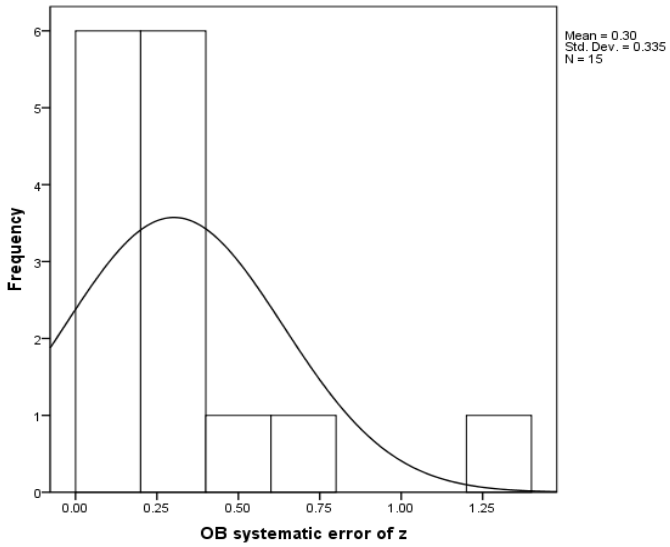

Figure: 4. 8: Systematic errors measured by OBI in the z direction in cm.

Figure 4.8 shows the histogram of the systematic errors of OBI in the antereoposterior direction and the graph shows that most of the errors were within 0.5cm and three patients had an error of >0.5cm (0.6, 0.63 and 1.30cm).

4.2.2.2 POPULATION SYSTEMATIC ERROR OBI

Systematic	No of	Overall population mean set	Population Systematic
X	15	0.22	0.05
y	15	0.28	0.1
Z	15	0.3	0.12

Table 4.2.2.2: Overall Population Mean Setup Error and the Population Systematic using OBI.

The Overall Population Systematic Error was 0.05, 0.1 and 0.12 in the x, y and z directions respectively as shown in Table 4.2.2.2.

4.2.3: COMPARISON OF CBCT AND OBI SYSTEMATIC ERRORS

CBCT Vs OBCT	Bias [SD]	Limits of Agreement
Systematic error(x)	-0.07[0.19]	[-0.44, 0.30]
Systematic error(y)	0.016[0.15]	[-0.28, 0.31]
Systematic error(z)	-0.20[0.31]	[-0.80, 0.41]

Table 4.2.3.1: Shows the Bias and the limits of agreement between the OBI and CBCT systematic errors.

The Bland-Altman plot was used for the comparison between the two modalities, in which the differences are plotted against the averages of the two modalities. Horizontal lines are drawn at the mean difference, and at the limits of agreement which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences.

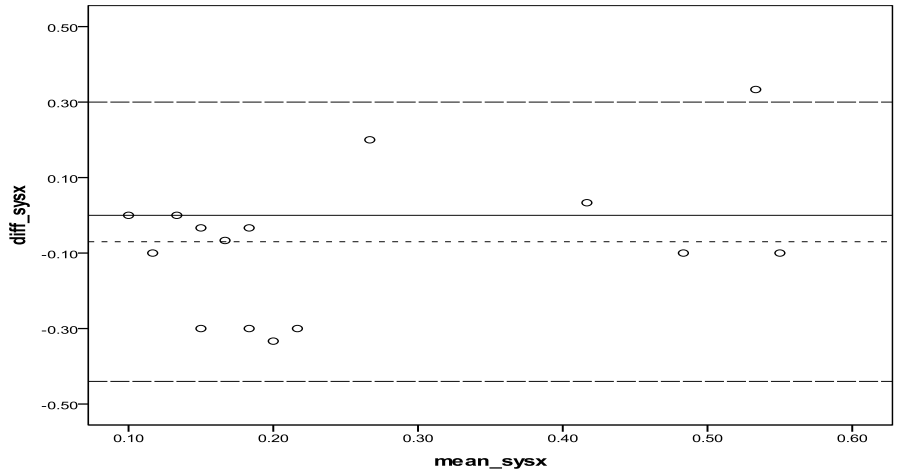

Figure: 4. 9: The Bland-Altman plot between the CBCT and OBI in the x direction.

In Table 4.2.3.1 and Figure 4.9 the Bland–Altman plot for the systematic error in the x direction showed a bias of -0.07 with an agreement limit of (-0.44, 0.30). This suggests that the CBCT and OBI do not have a good agreement with each other and there is 1 patient who is not within the limits.

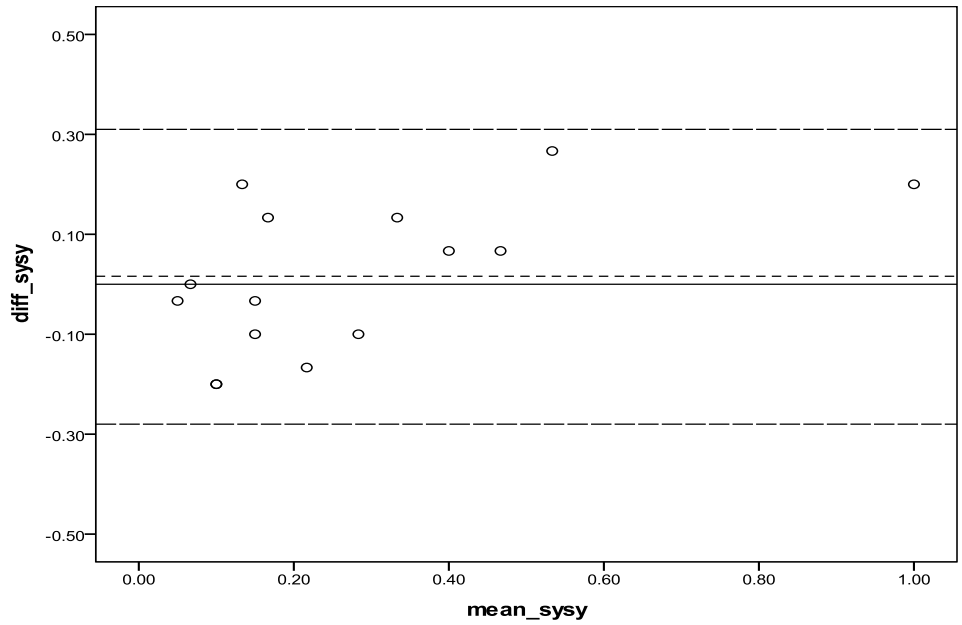

Figure: 4. 10: The Bland-Altman plot between the CBCT and OBI in the y direction

In Table 4.2.3.1 and Figure 4.10 the Bland–Altman plot for the systematic error in the y direction showed a bias of 0.01 with an agreement limit of (-0.28, 0.31).This suggests that the CBCT and OBI do not have a good agreement with each other.

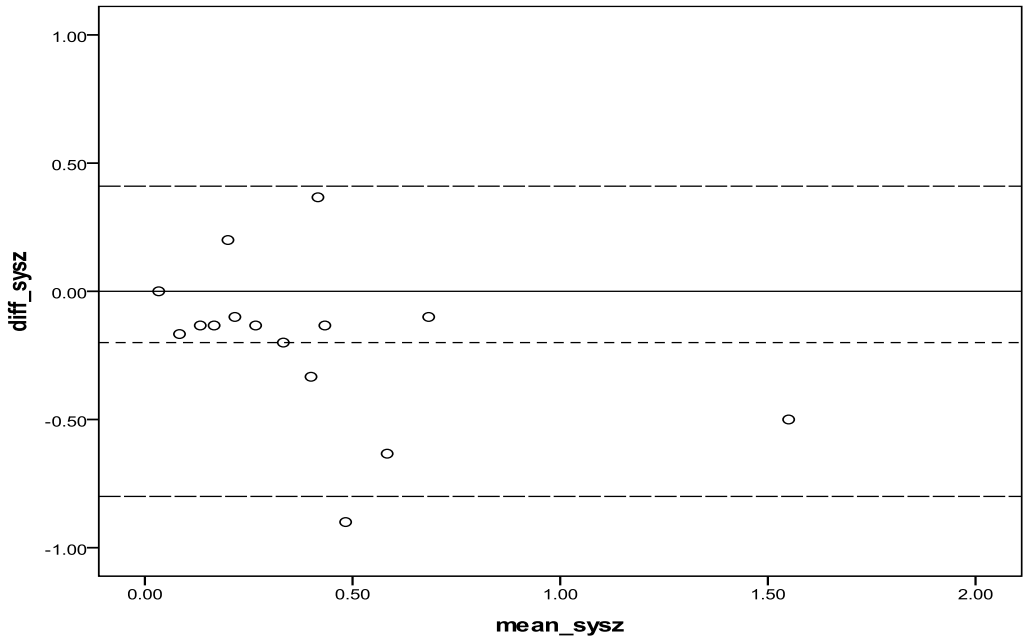

Figure: 4. 11 : The Bland-Altman plot between the CBCT and OBI in the z direction

Table 4.2.3.1 and Figure 4.11 the Bland–Altman plot for the systematic error in the z direction showed a bias of -0.20 with an agreement limit of (-0.80, 0.41). This suggests that the CBCT and OBI do not have a good agreement with each other. One patient was out of the limits.

	CBCT			OBI			
	Minimum	**Median**	**Maximum**	**Minimum**	**Median**	**Maximum**	**p**
Sys	0.10	0.30	0.60	0.00	0.13	0.70	0.10
Sys	0.03	0.20	0.90	0.00	0.23	1.10	0.68
Sys	0.03	0.33	1.80	0.00	0.23	1.30	0.03

Table 4.2.3.2: The Systematic Error had a value of 0.03 which was significant in the z direction.

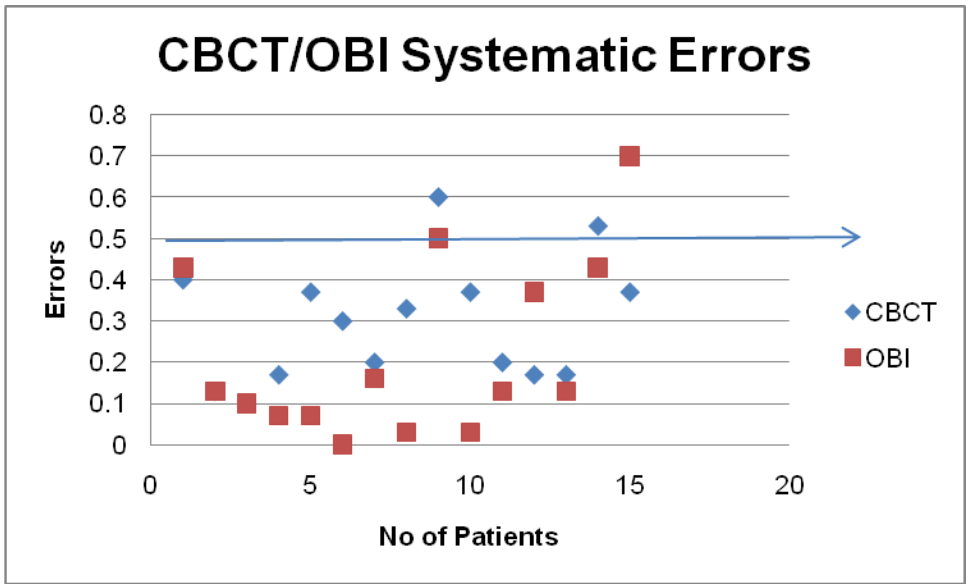

Figure: 4. 12 : Comparison of CBCT and OBI systematic errors in x direction in cm.

Comparison between systematic errors in CBCT and OBI in the x direction showed that two patients in CBCT and one patient in the OBI exceeded the tolerance of 5mm as depicted in the Figure 4.12.

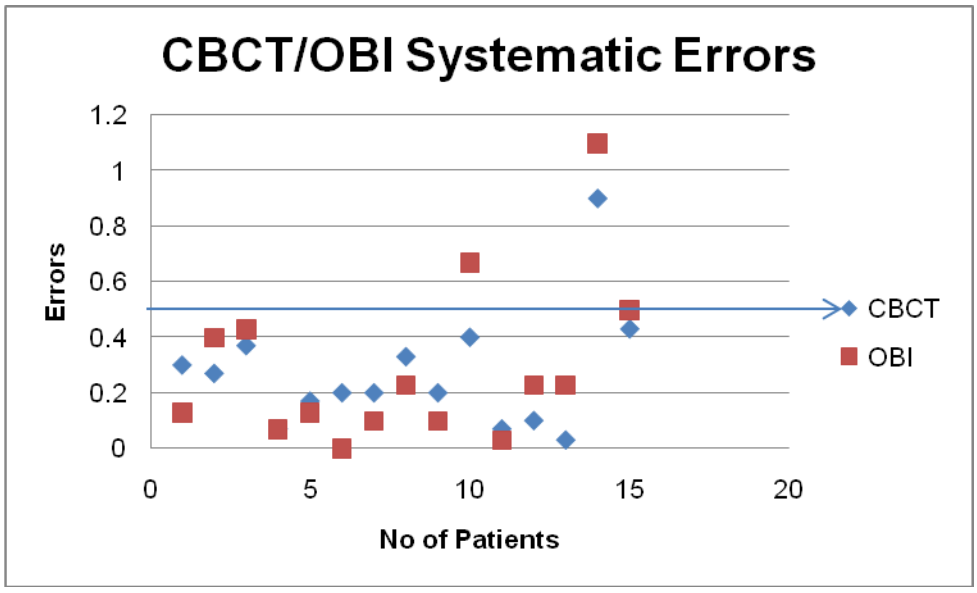

Figure: 4. 13: Comparison of CBCT and OBI systematic errors in y direction in cm.

Comparison between systematic errors in CBCT and OBI in the y direction showed that one patient in the CBCT and two patients in the OBI exceeded the tolerance of 5mm as depicted in the Fig. 4.13.

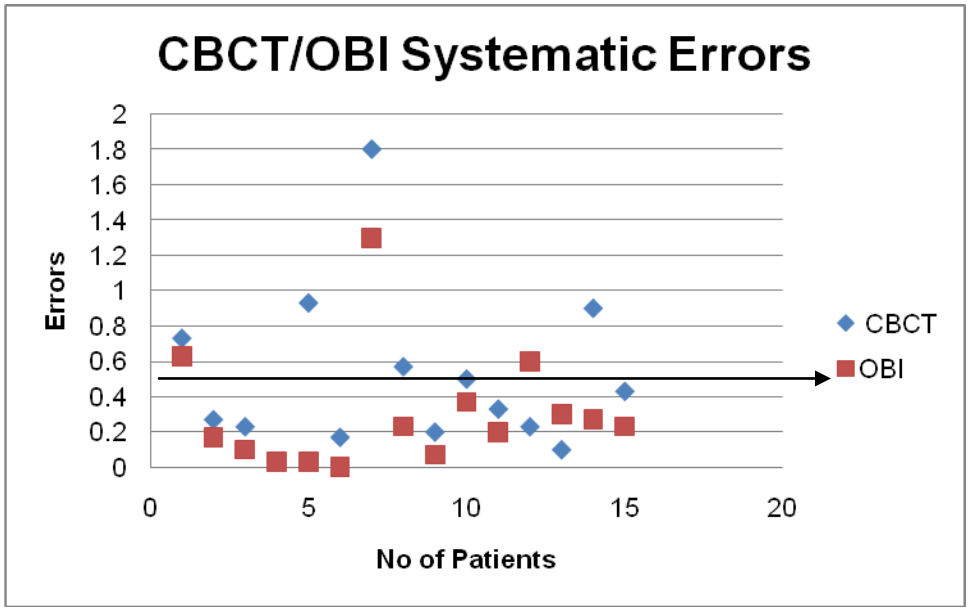

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Figure: 4. 14: Comparison of CBCT and OBI systematic errors in z direction in cm.

Comparison between the systematic errors of CBCT and OBI in the z direction showed that 5 patients in CBCT and 3 patients in OBI exceeded the tolerance limits of 5 mm as shown in Fig 4.14.

4.2.4 CONE BEAM COMPUTED TOMOGRAPHY

4.2.4.1 RANDOM ERRORS:

Definition: They are deviations between different fractions, during a treatment series which are a result of day to day variation in patient position and organ motion or otherwise called treatment execution errors.

Patient No:	x[cm]	y[cm]	z[cm]	Radial Error
1	0.15	0.10	0.24	0.3
2	0.12	0.21	0.15	0.277
3	0.17	0.26	0.12	0.33
4	0.09	0.18	0.18	0.27
5	0.16	0.22	0.22	0.34
6	0.23	0.36	0.14	0.44
7	0.10	0.38	0.16	0.47
8	0.17	0.47	0.63	0.80
9	0.31	0.31	0.51	0.67
10	0.15	0.56	0.40	0.70
11	0.12	0.27	0.47	0.55
12	0.71	0.45	0.16	0.85
13	0.13	0.26	0.25	0.38
14	0.17	0.46	0.36	0.60
15	0.47	0.32	0.30	0.48
Mean	0.2168	0.3079	0.3032	0.6853
SD	0.1657	0.1289	0.4156	0.45318
Min	0.09	0.10	0.12	0.18
Max	0.71	0.56	0.63	1.82
Percentile	Quantiles			
25^{th}	0.1225	0.2128	0.1590	0.3944
50^{th}[median]	0.1633	0.2693	0.2539	0.6633
75^{th}	0.2279	0.4466	0.4197	0.8876

Table 4.2.4.1: Random Errors in cm in x, y and z direction and radial errors using CBCT

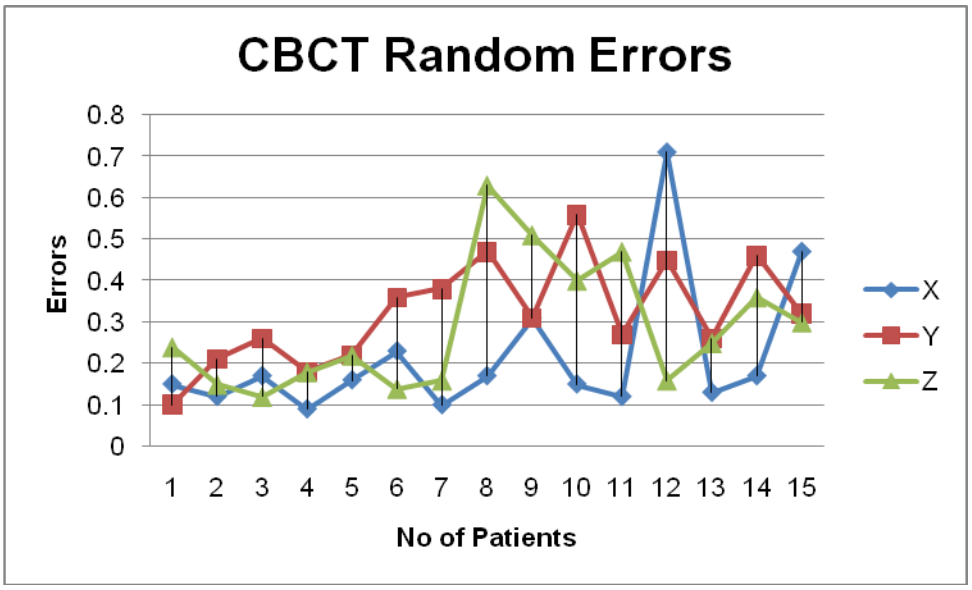

Figure: 4. 15: Random Errors measured by CBCT in cm in x, y and z directions for the 15 patients.

The random errors of the CBCT ranged from 0.09 to 0.71cm in the x direction, 0.10 to 0.56cm in the y direction and 0.12 to 0.63cm in the z direction respectively. The shift exceeded the tolerance in 1 patient in x direction, 1 patient in the y direction and 2 patients in z direction. The median shift and shift in 75th percentile were within the tolerance.

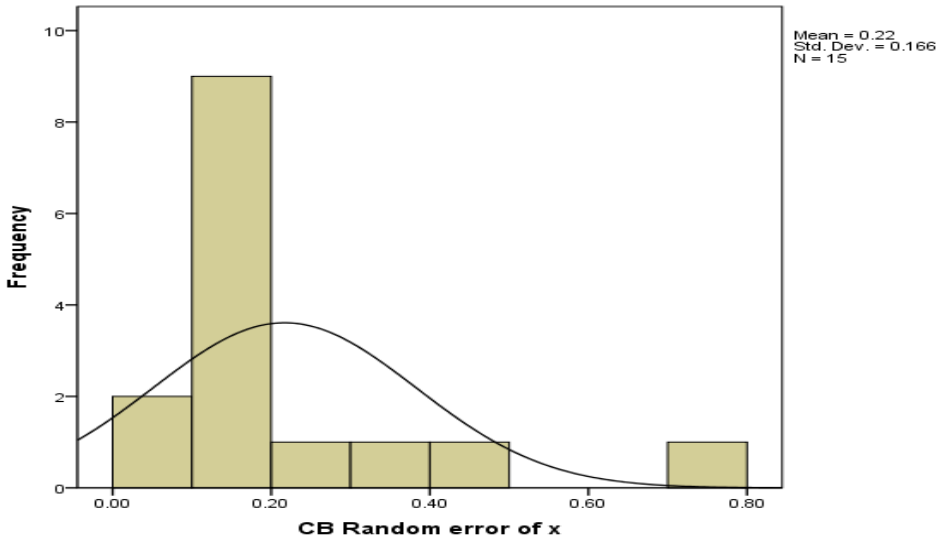

Figure: 4. 16: Random Errors measured by CBCT in the x direction in cm

Figure 4.16 shows the histogram of the random errors of CBCT in the mediolateral direction and the graph shows that most of the errors were within 0.5cm. One patient had an error of more than 0.5cm (0.71cm).

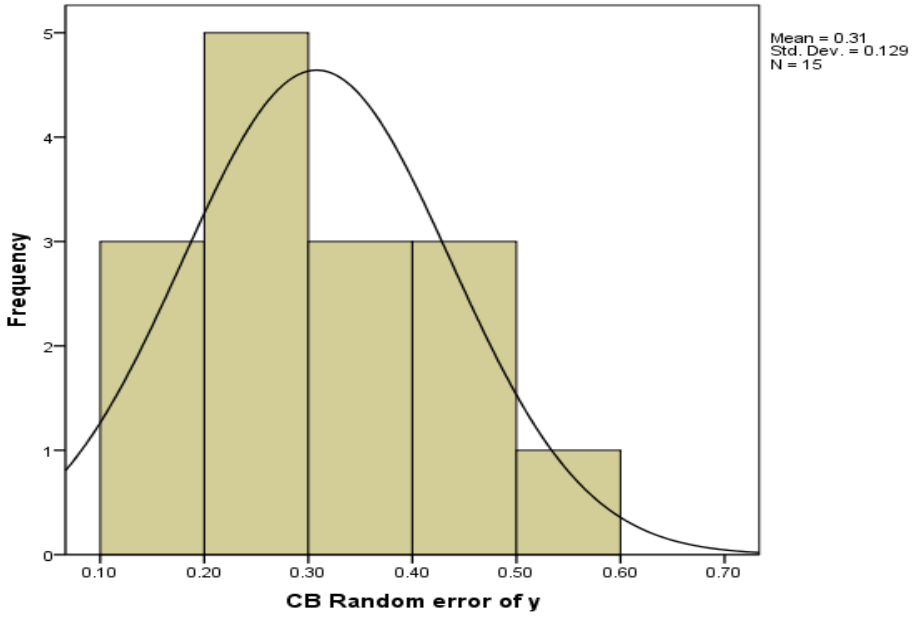

Figure: 4. 17: Random Errors measured by CBCT in the y direction in cm

Figure 4.17 shows the histogram of the random errors of CBCT in the craniocaudal direction and the graph shows that most of the errors were within 0.5cm except for one patient who had an error of 0.56cm. The graph represents a normal distribution.

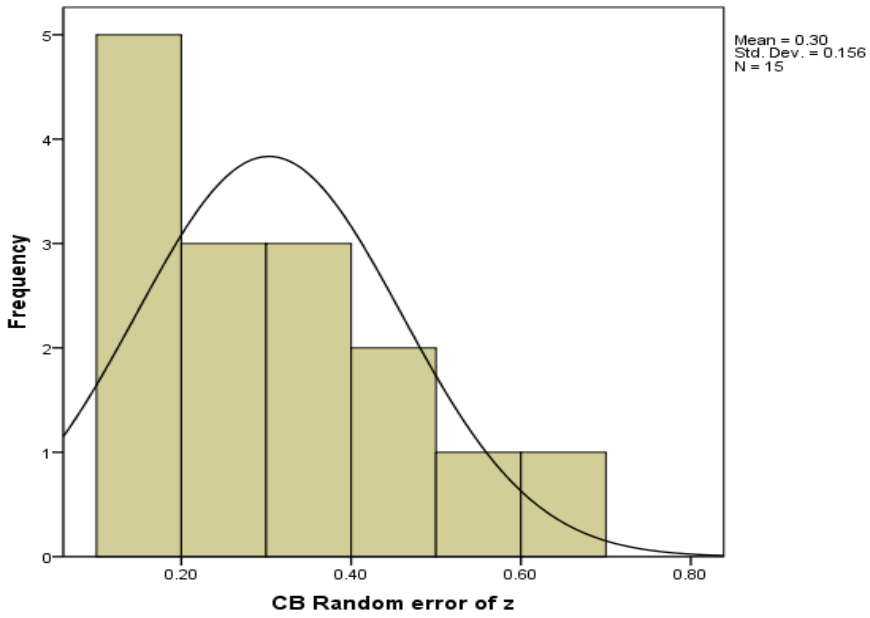

Figure: 4. 18: Random Errors measured by CBCT in the z direction in cm

Figure 4.18 shows a histogram of the random errors of CBCT in antereoposterior direction and the graph shows that 13 patients had errors within 0.5cm, 2 patients had an error of 0.51 and 0.63cm.

4.2.4.2 POPULATION RANDOM ERROR CBCT

Random Error	No of Patients	Population Random Error $\sigma_{set\text{-}up}$
x	15	0.22
y	15	0.31
z	15	0.30

Table 4.2.4.2: Population Random Error [$\sigma_{set\ up}$] using CBCT

The population random errors were 0.22, 0.31 and 0.30 in the x, y and z direction.

4.2.5 ON BOARD IMAGER

4.2.5.1 RANDOM ERRORS

Patient No.	x [cm]	y [cm]	z [cm]	Radial Error
1	0.34	0.31	0.32	0.56
2	0.11	0.13	0.17	0.240
3	0.21	0.17	0.31	0.411
4	0.39	0.21	0.24	0.503
5	0.24	0.23	0.00	0.332
6	0.25	0.25	0.07	0.360
7	0.09	0.17	0.30	0.356
8	0.25	0.57	0.39	0.734
9	0.23	0.17	0.30	0.414
10	0.24	0.48	0.00	0.536
11	0.11	0.28	0.36	0.469
12	0.22	0.22	0.27	0.411
13	0.11	0.22	0.26	0.357
14	0.24	0.54	0.46	0.748
15	0.47	0.25	0.29	0.611
Mean	0.2333	0.2814	0.2501	0.5566
SD	0.1054	0.1740	0.1732	0.2427
Min	0.09	0.13	0.00	0.0
Max	0.47	0.57	0.46	1.31
Percentile	Quantiles			
25^{th}	0.1130	0.1740	0.1732	0.2427
50^{th}[median]	0.2398	0.2345	0.3140	0.4558
75^{th}	0.2489	0.3140	0.3193	0.7789

Table 4.2.5.1: Random and Radial Errors in cm in the x, y and z directions by OBI

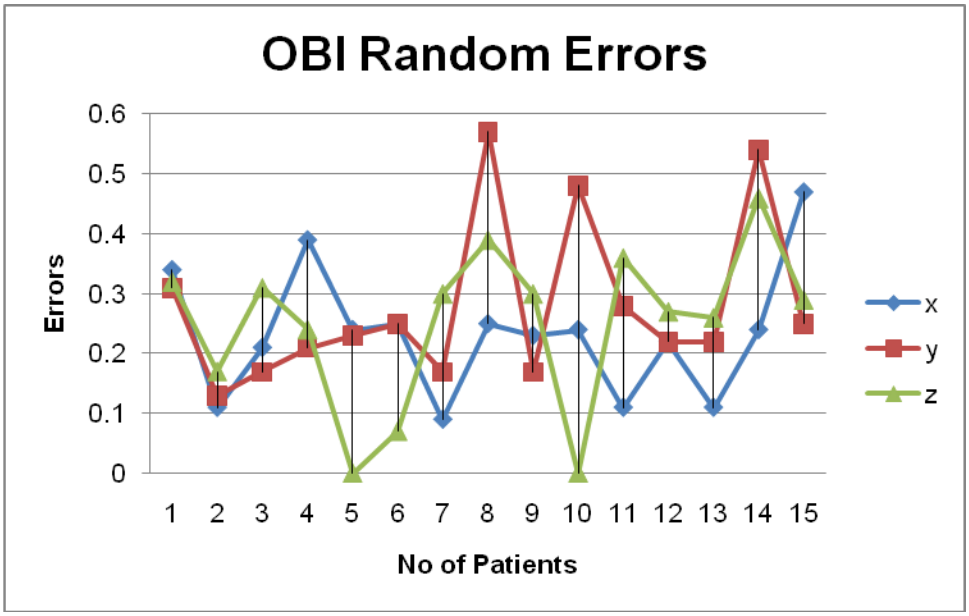

Figure: 4. 19: Random Error displacements in cm in the x, y and z direction for all 15 patients using OBI.

The Random Errors of the OBI ranged from 0.09 to 0.47cm in the x direction, 0.13 to 0.57cm in the y direction and 0.0 to 0.46cm in the z direction respectively as shown in Table 4.2.5.1. The maximum error was seen in one patient of 0.57cm in the y direction. The median shift and shift in 75th percentile were within the tolerance in all three directions.

4.2.5.2 POPULATION RANDOM ERROR OBI

Random Error	No of Patients	Population Random Error $\sigma_{set\text{-}up}$
x	15	0.23
y	15	0.28
z	15	0.25

Table 4.2.5.2: Population Random Error [$\sigma_{set\ up}$] using OBI

The population random errors were 0.23, 0.28 and 0.25 in the x, y and z direction respectively.

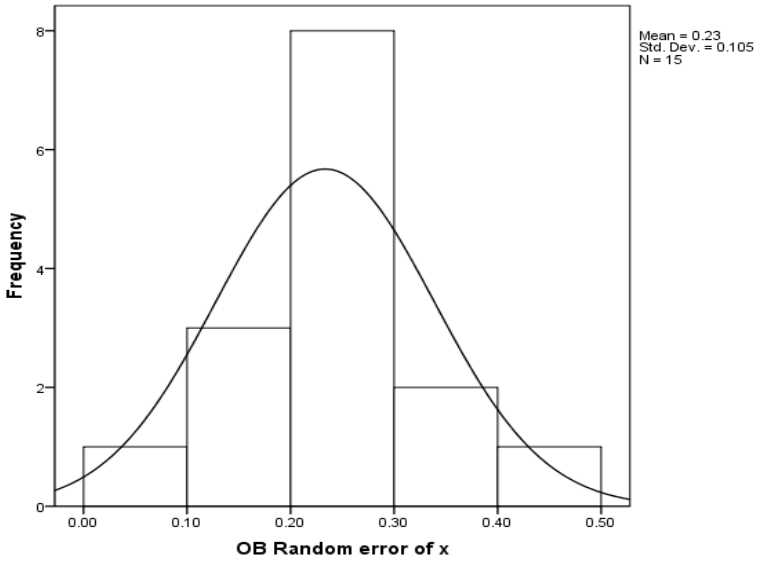

Figure 4.20: Random errors measured by OBI in the x direction in cm

Figure 4.20 shows a histogram of the random errors of OBI in mediolateral direction and the graph shows that all 15 patients had errors within 0.5cm.

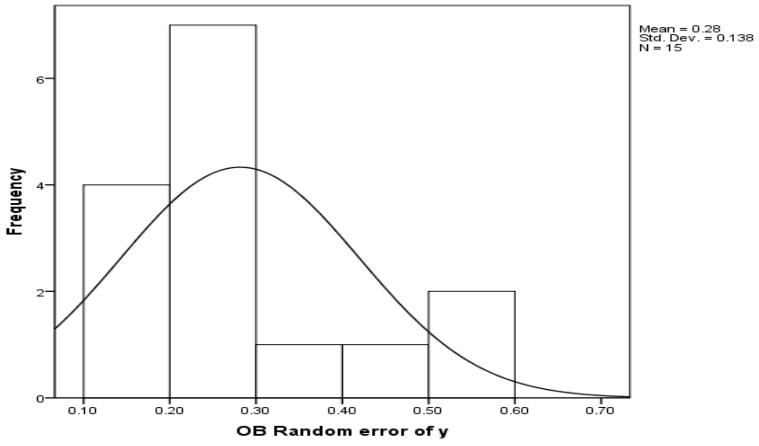

Figure 4.21: Random errors measured by OBI in the y direction in cm

Figure 4.21 shows a histogram of the random errors of OBI in craniocaudal direction and the graph shows that 14 patients had errors within 0.5cm, 1 patient had an error of 0.57.

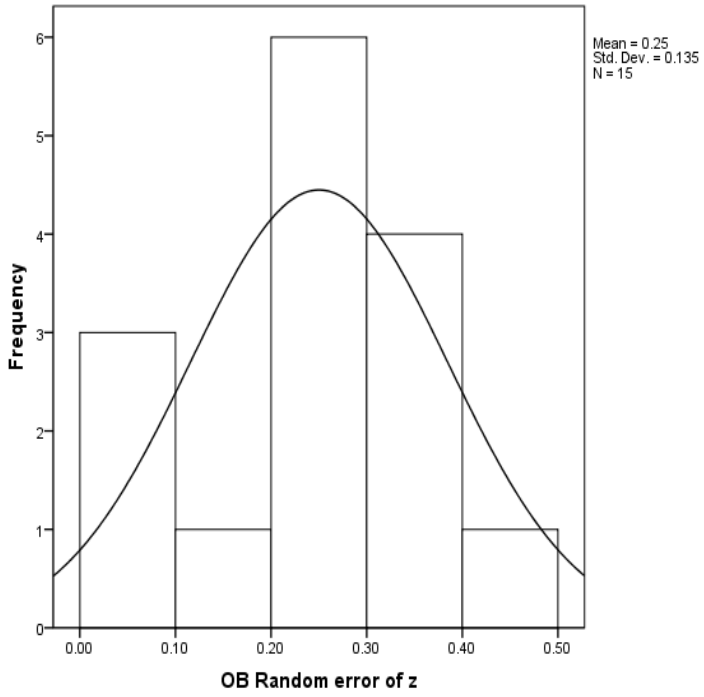

Figure 4.22: Random errors measured by OBI in the z direction in cm

Figure 4.22 shows a histogram of the random errors of OBI in antereoposterior direction and the graph shows that all 15 patients had errors within 0.5cm.

4.2.6 COMPARISON OF CBCT AND OBI RANDOM ERRORS

CBCT Vs OBCT	BIAS[SD]	Limits of Agreement
Random error(x)	0.02[0.17]	[-0.31, 0.35]
Random error(y)	0.03[0.11]	[-0.25, 0.19]
Random error(z)	-0.05[0.16]	[-0.36, 0.26]

Table 4.2.6.1: Shows the Bias and the limits of agreement between the CBCT and OBI random error

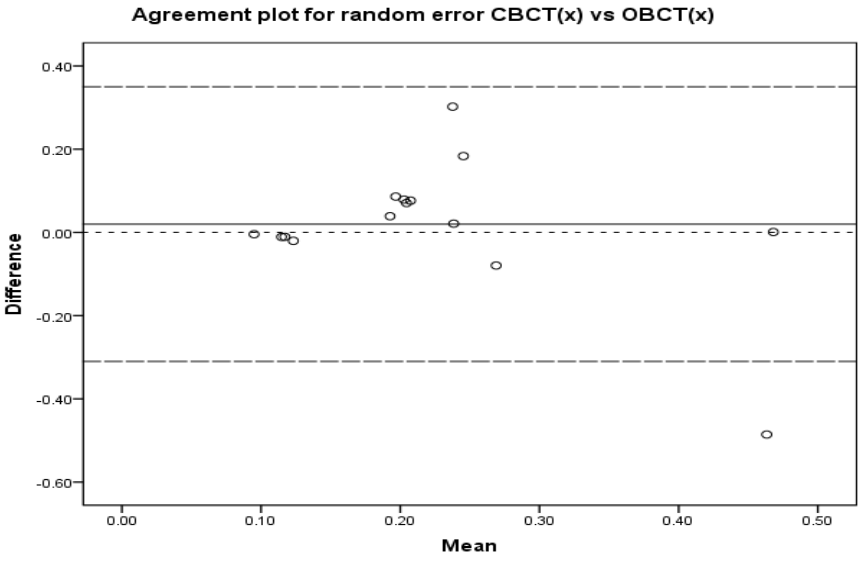

Figure: 4. 23: The Bland-Altman plot between the CBCT and OBI in the x direction.

Table 4.2.6.1 and Figure 4.23 the Bland–Altman plot for the random error in the x direction showed a bias of 0.02 with an agreement limit of (-0.31, 0.35). This suggests that the CBCT and OBI do not have a good agreement with each other. One patient was out of the limits.

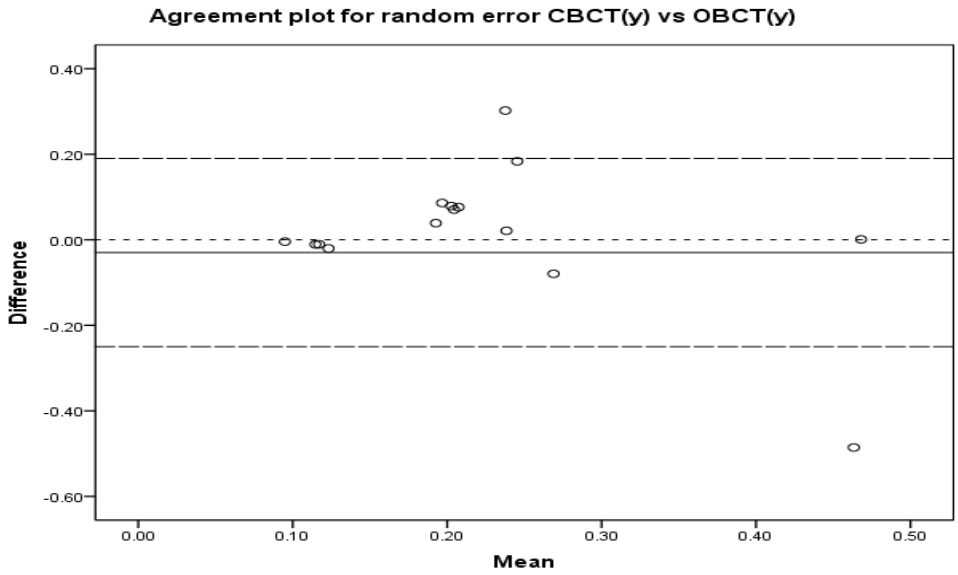

Figure: 4. 24: The Bland-Altman plot between the CBCT and OBI in the y direction

Table 4.2.6.1 and Figure 4.24 the Bland–Altman plot for the random error in the y direction showed a bias of 0.03 with an agreement limit of (-0.25, 0.19).This suggests that the CBCT and OBI do not have a good agreement with each other. Two patients were not within the limits.

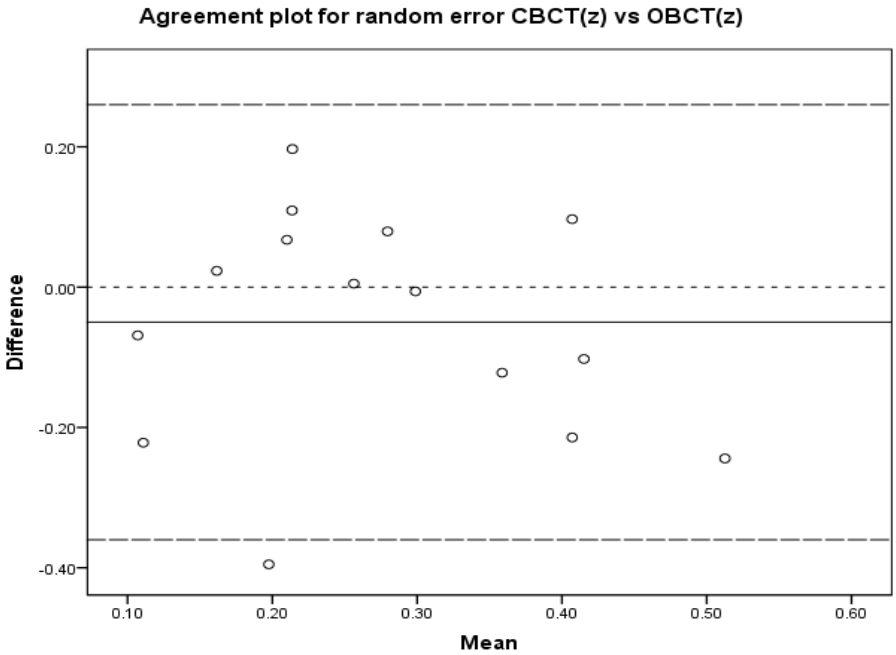

Figure: 4. 25: The Bland-Altman plot between the CBCT and OBI in the z direction

Table 4.2.6.1 and Figure 4.25 the Bland–Altman plot for the random error in the y direction showed a bias of -0.05 with an agreement limit of (-0.36, 0.26). This suggests that the CBCT and OBI do not have a good agreement with each other. One patient was not within the limits.

	CBCT			OBI			
	Minimum	**Median**	**Maximum**	**Minimum**	**Median**	**Maximum**	**p Value**
Ran err x	0.09	0.16	0.71	0.09	0.23	0.47	0.25
Ran err y	0.10	0.26	0.56	0.13	0.23	0.57	0.25
Ran err z	0.12	0.25	0.63	0.00	0.31	0.46	0.28

Table 4.2.6.2: The p value was not statistically significant for Random Errors in any direction [p value of ≤ 0.05 was taken as significant].

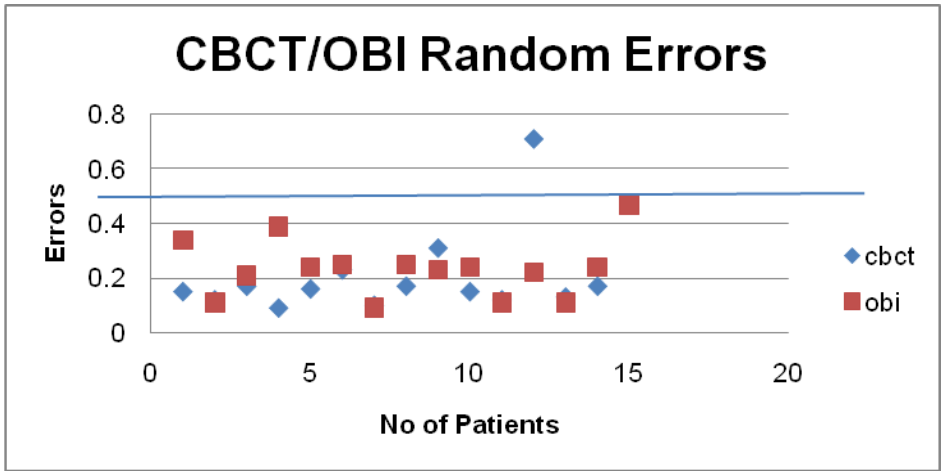

Figure: 4. 26: Comparison of CBCT and OBI random errors in the x direction in cm

The comparison between the CBCT and the OBI random errors in the x direction showed that only one patient in the CBCT was above the tolerance of 5mm as shown in figure 4.26

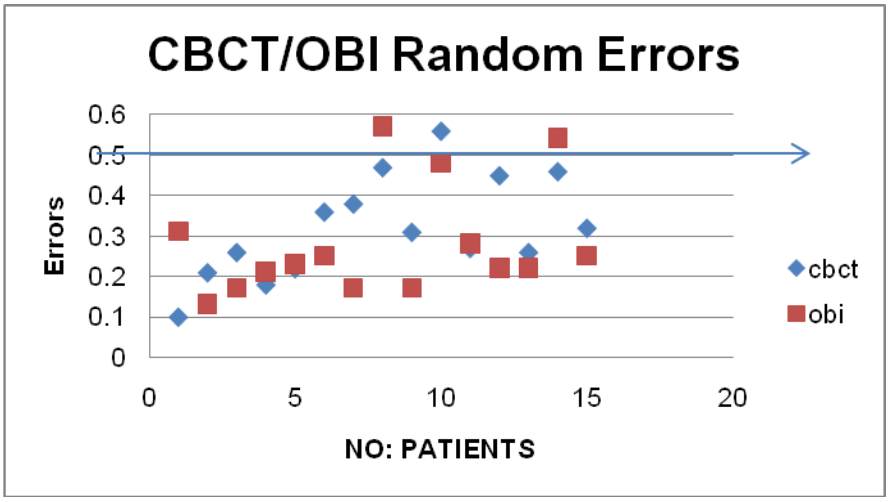

Figure: 4. 27: Comparison of CBCT and OBI random errors in the y direction in cm.

The comparison of the CBCT and the OBI random errors in the y direction showed that one patient in CBCT and two patients in OBI were above the tolerance of 5mm as shown in Figure 4.27.

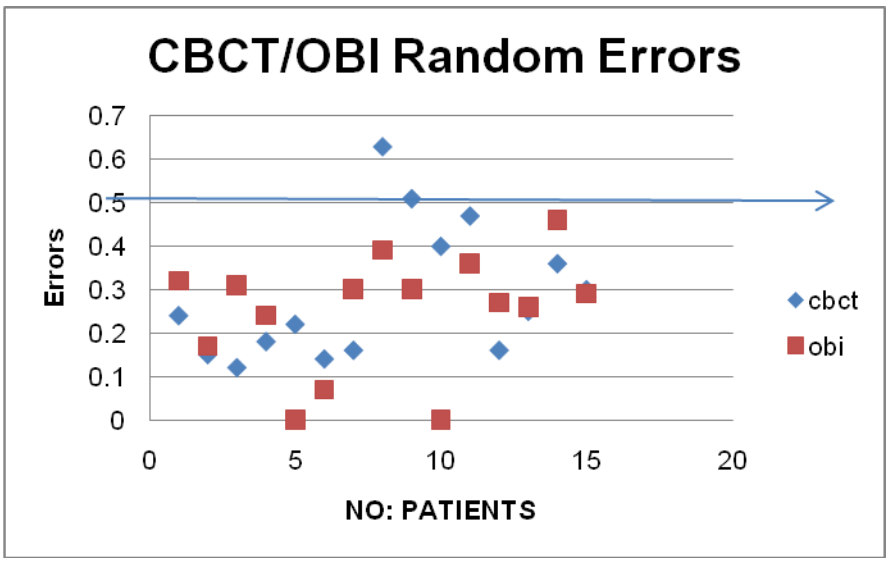

Figure: 4. 28: Comparison of CBCT and OBI Random Errors in the z direction in cm

The comparison between the CBCT and the OBI Random Errors in the z direction showed only one patient in the CBCT more than the tolerance of 5 mm as shown in Figure 4.28.

4.2.7 VECTOR DISPLACEMENT

4.2.7.1 SYSTEMATIC RADIAL ERROR: CBCT

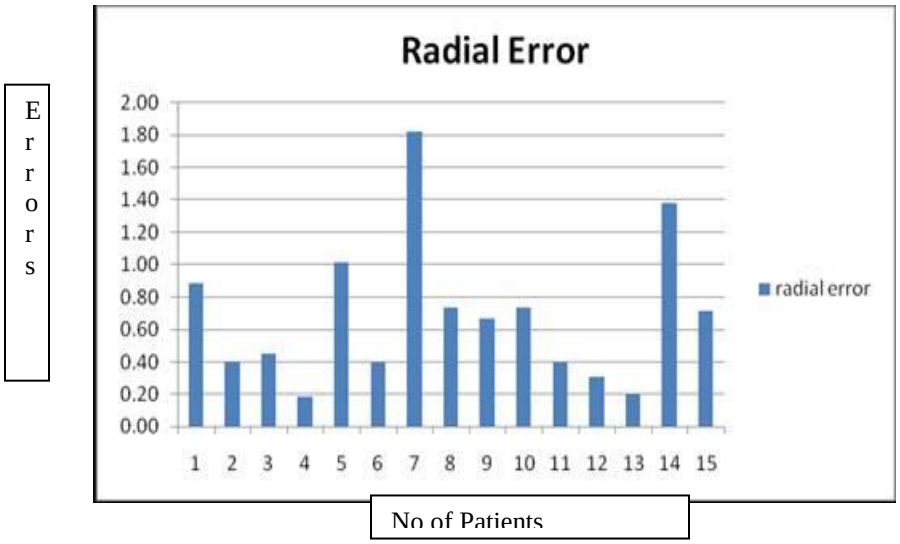

Figure: 4. 29: CBCT: Length of the Mean Vector Displacement in cm

Figure 4.29 show that the Radial Systematic Errors ranged from 0.18 to 1.82cm for the CBCT

4.2.7.2 SYSTEMATIC RADIAL ERROR: OBI

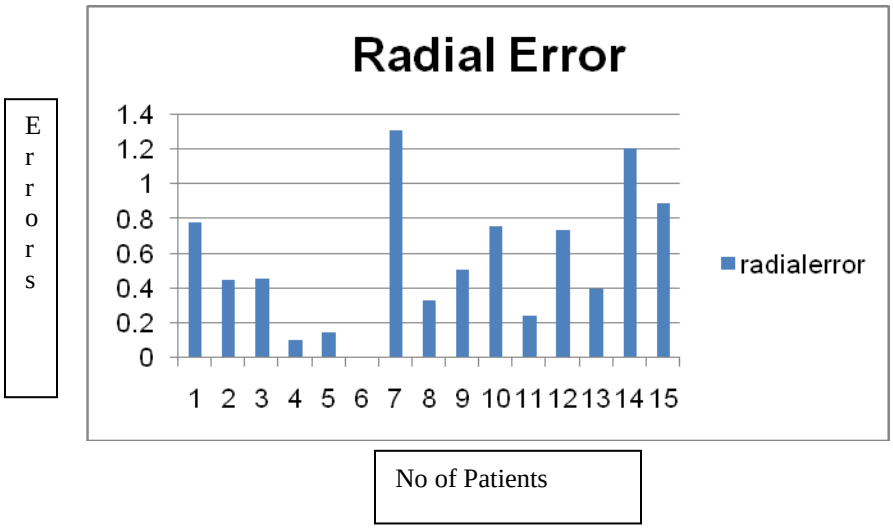

Figure: 4. 30: OBI: Length of the Mean Vector Displacement in cm

The radial errors as shown in Fig 4.30 show that the Radial Systematic Errors ranged from 0.0 to 1.31cm for the OBI.

4.2.7.3 RANDOM RADIALERRORS: CBCT

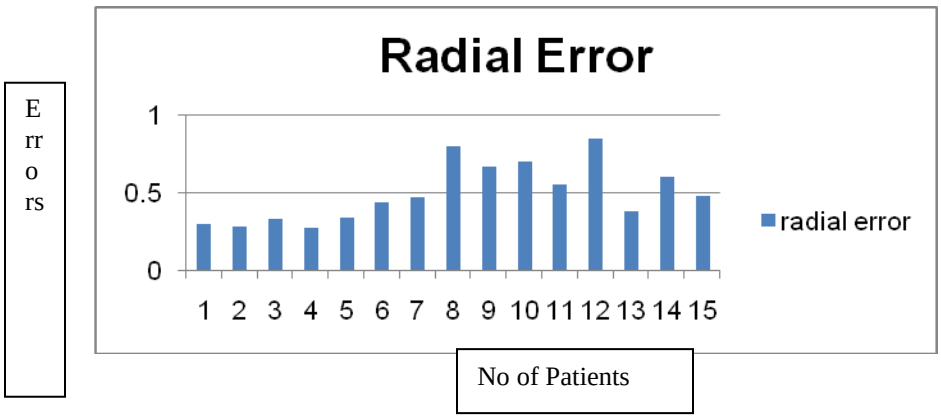

Figure: 4. 31: CBCT: Length of the mean vector displacement in cm

The Radial Random Errors shown in Figure 4.31 ranged from 0.27 to 0.85cm in CBCT.

4.2.7.4. RANDOM RADIALERRORS: OBI

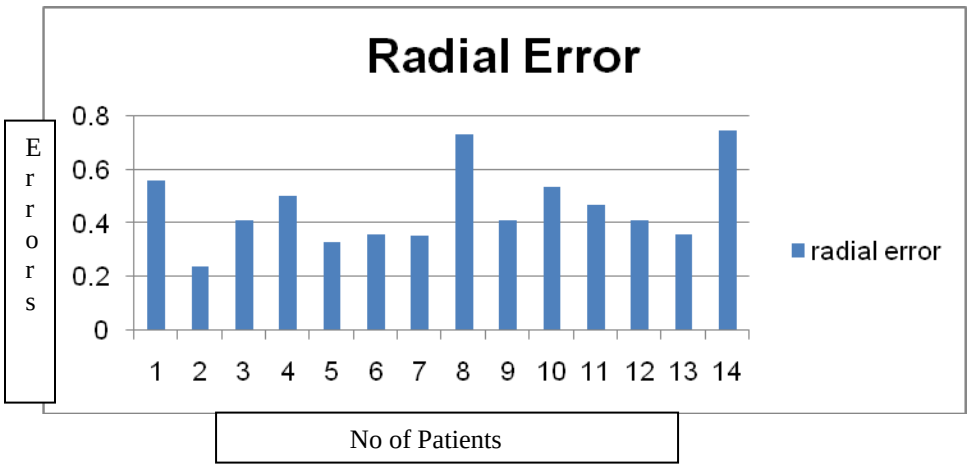

Figure: 4. 32: OBI: Length of the mean vector displacement in cm

The Radial Random Errors shown in Figure 4.32 ranged from 0.24 to 0.74cm in OBI.

4.2.8 COMPARISON OF RADIAL ERRORS BETWEEN CBCT AND OBI

4.2.8.1 SYSTEMATIC ERRORS

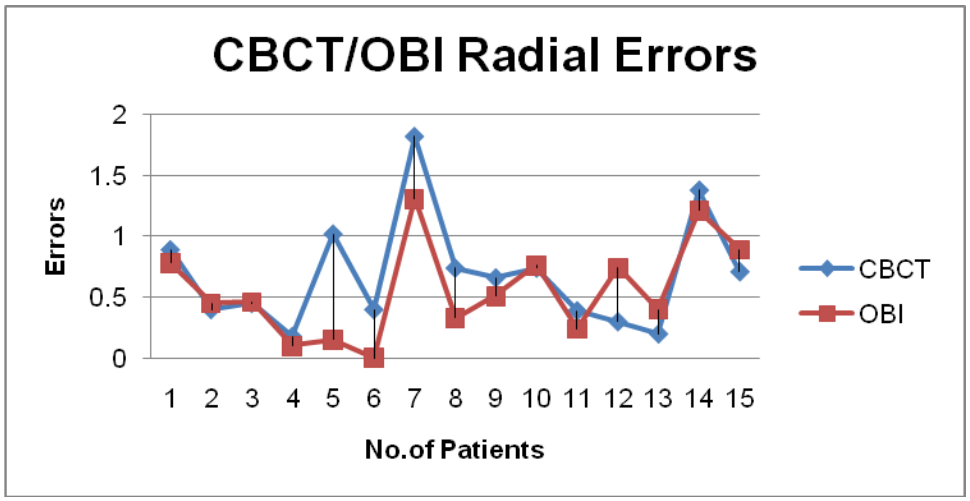

Figure: 4. 33: Comparison of the Radial Systematic Errors between CBCT and OBI.

The Radial Systematic Errors were compared between the OBI and CBCT and Figure 4.33 shows trend of errors between the two modalities. This figure shows that the CBCT detected more number of errors than the OBI.

4.2.8.2 RANDOM ERRORS

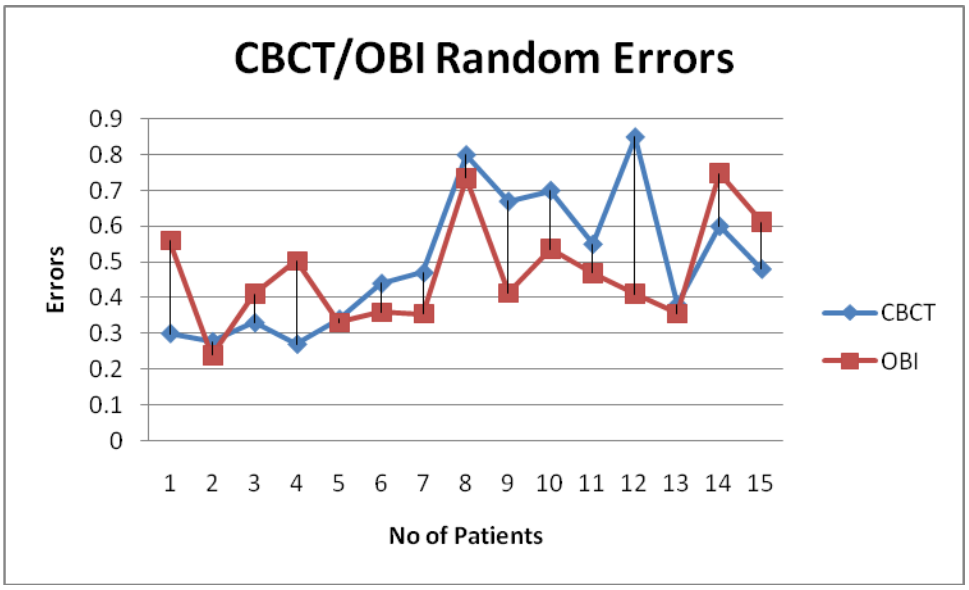

Figure: 4.34 Comparison of the Radial Random Errors between CBCT and OBI

The Radial Random Errors were compared between the OBI and CBCT in the Fig 4.31 shows trend of errors between the two modalities. This Figure shows that CBCT detected more errors as compared to the OBI.

Radial Error				
	Minimum	**Median**	**Maximum**	**P Value**
CBCT	0.18	0.66	1.82	0.21
OBI	0.00	0.45	1.31	

Table 4.2.8.3: Comparison between the radial errors of CBCT and OBI.

It gives a P value of 0.21 which is not significant. [<0.05 is considered as significant]

CBCT Vs OBCT	BIAS[SD]	Limits of Agreement [LL, UL]
Radial error	-0.13[0.32]	[-0.76, 0.5]

Table 4.2.8.4: Radial error between the CBCT and OBI with the Bias and the limits of agreement

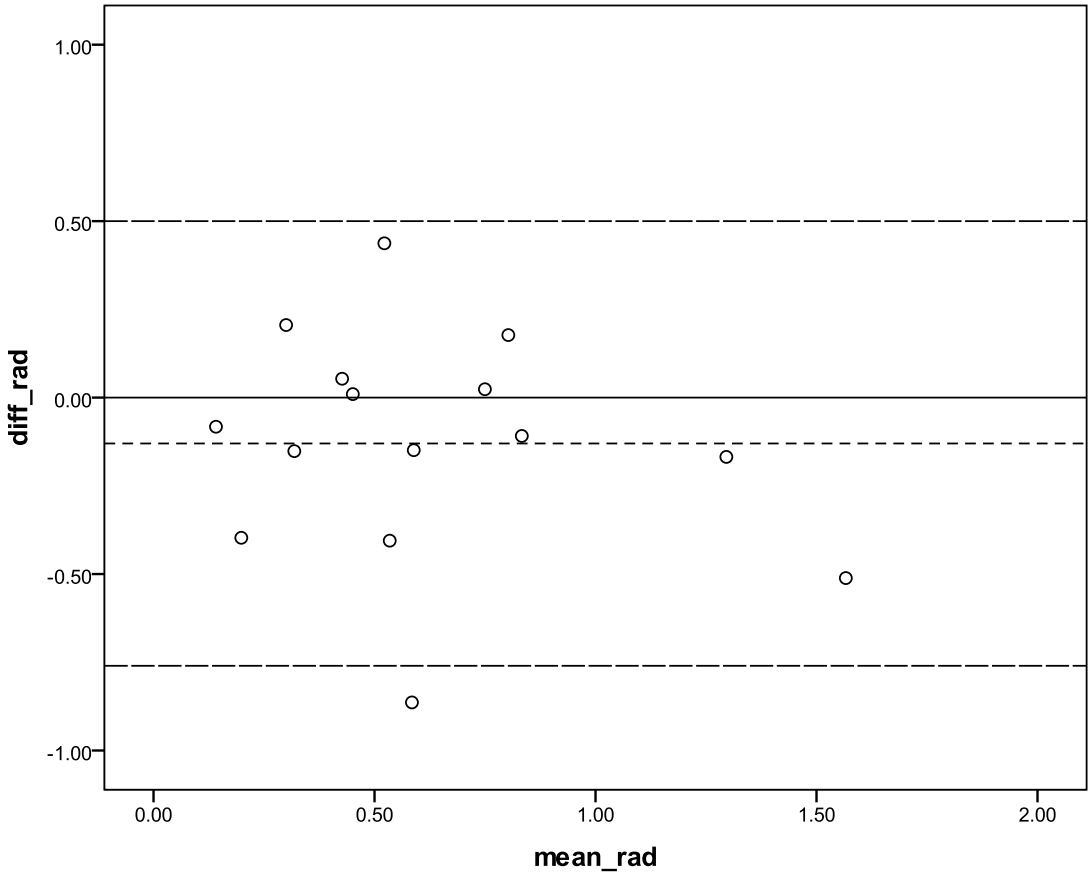

Figure: 4. 35: This shows the Bland-Altman plot for the Radial Error comparing the CBCT and the OBI.

Table 4.3.2 and Figure 4.32 the Bland–Altman plot for the radial error between CBCT and OBI which showed a bias of -0.13 with an agreement limit of (-0.76, 0.5). This suggests that the CBCT and OBI do not have good agreement with each other. One patient was not within the limits.

4.4 CALCULATION OF CTV TO PTV MARGIN.

The calculation of the CTV to PTV margin was done using the formulas which are given below where Σ is the Population systematic error and σ is the Population random error.

1. Van Herk's formula: $2.5\Sigma + 1.64\ \sigma$
2. Stroom's formula: $2\Sigma + 0.7\sigma$
3. ICRU formula: $\Sigma + 0.7\sigma$

		CBCT			OBI	
	VAN HERK	**STROOM**	**ICRU**	**VAN HERK**	**STROOM**	**ICRU**
X	0.41	0.19	0.17	0.50	0.26	0.21
Y	0.60	0.25	0.25	0.70	0.39	0.29
Z	1.04	0.65	0.43	0.71	0.41	0.29

The above Table 4.4.1 shows that in the Van Herk formula,the margins were not adequate in the y and z direction and in the Stroom's formula the margins were not adequate only in the z direction.[CTV to PTV margin in our institution was taken as 0.5cm for pelvic malignancies].

4.5) TIME TREND ANALYSIS:

The time trend analysis is a necessary tool to assess the changes in errors with time in turn enabling the adequacy of treatment.

This was calculated as an average of the total errors every week and plotted against time.

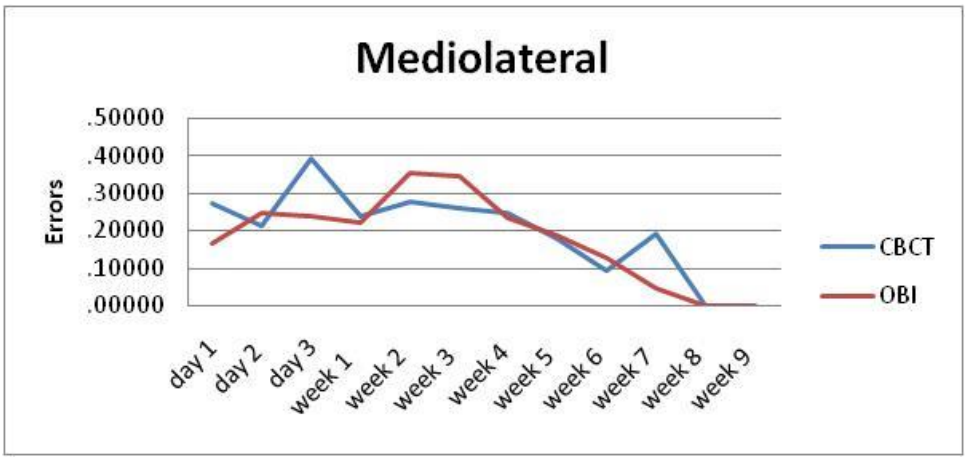

Figure: 4. 36: This shows the time trend of CBCT versus OBI in the x direction.

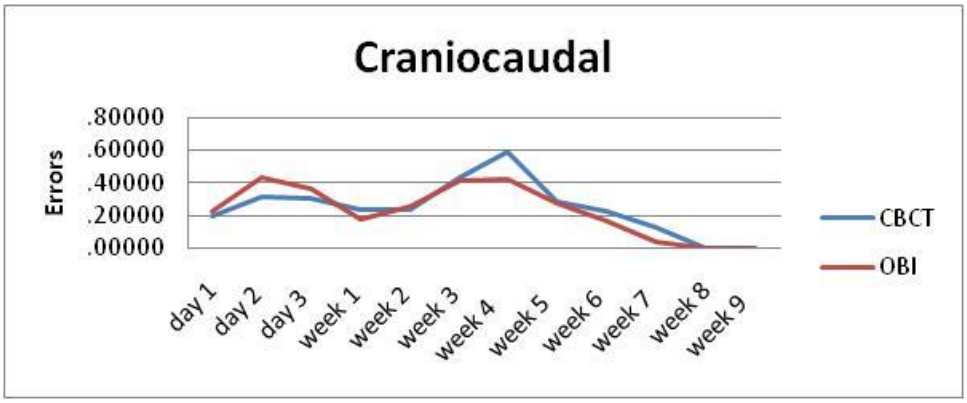

Figure: 4. 37: This figure shows the time trend of CBCT versus OBI in the y direction.

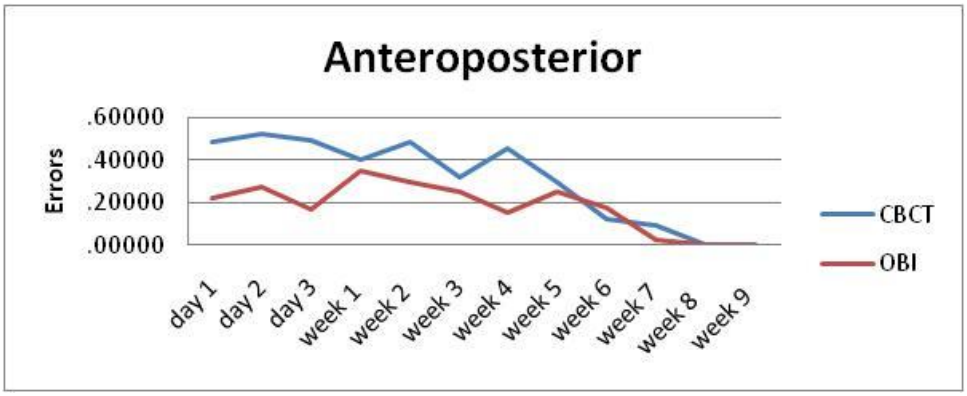

Figure: 4. 38: This figure shows the time trend of CBCT versus OBI in the z direction

The time trend analysis depicts that the errors measured by CBCT and the OBI were almost equal in the x and y direction, but in the z direction there were more errors detected by CBCT as compared to the OBI.

6. DISCUSSION

6.1. INTRODUCTION

The set up of patients before initiation of radiation treatment is an important aspect in the planning process and later in the treatment process. Errors during the set up contribute to the in adequacy in dose delivered to the target as well as the surrounding normal organs.

A good IG-IMRT protocol reduces these set up errors, thus resulting in a more precise set up and treatment delivery. We should also ensure that the modality of imaging is adequate for treatment verification thereby avoiding unnecessary dose to the patient with repeat imaging.

This study was performed to compare between the two modalities of imaging, Kilo Voltage Cone Beam CT [KV CBCT] and the On Board Imager [OBI] which are used for verifying the position of the patient prior to treatment delivery.

It used the 3D-3D matching and the 2D-2D matching respectively. The systematic and the random errors were calculated based on the shifts noted. According to the ICRU, the CTV to PTV margins should represent the real dose in the "moving" Clinical Target Volume(31).

The calculations of CTV to PTV margin based on the Systematic and the Random Errors were proposed by various authors but it is important for each institution to have its own protocol for the same. This study also aims to calculate the CTV to PTV margins based on the 2 modalities of treatment verification.

6.2. ERRORS

6.2.1. CONE BEAM CT SCAN

Studies have been done in pelvic malignancies on set up errors. Kim et al showed Systematic Errors of 0.21, 0.12 and 0.22cm and the Random Errors of 0.48, 0.30 and 0.38cm with CBCT in the mediolateral [ML], craniocaudal [CC] and antereoposterior [AP] directions respectively(39). Palombarini M et al(40) analysed the shifts using the kV CBCT and the Systematic Errors were <0.1cm in the ML and the CC directions, but 0.32cm in the AP direction. The Random Errors were also more in AP direction as compared to the ML and CC direction.

A study done by Zaghloul MS et al on CBCT showed Systematic Errors of 0.21 (±0.12), 0.30 (±0.21) and 0.22 (±0.18)cm and Random Errors of 0.21 (±0.16), 0.24 (±0.18) and 0.23 (±0.18)cm in the ML, CC and AP directions respectively(41).

Vanasek J et al(21) performed a study on adaptive image guided intensity modulated radiation therapy using kV CBCT and kV- kV imaging. More errors were seen in the AP direction with shifts of ≥0.2cm in 43% and ≥0.5cm in 9% of the patients. He proposed that integrating CBCT and kV-kV imaging in the IG-IMRT protocol provided adequate coverage of the target.

The study done by Kataria et al(42) to assess set up error using kV x- ray volume imaging in abdominal malignancies showed Systematic Errors of 0.11, 0.3 and 0.13cm and Random Errors of 0.2, 0.48 and 0.19cm in the ML, CC and AP directions respectively and a mean vector displacement of 0.35cm .

In our study the mean Systematic Errors calculated in the mediolateral [ML], craniocaudal [CC] and antereoposterior [AP] directions were 0.29 (±0.14), 0.2 (±0.45) and 0.50cm (±0.21) respectively as shown in Table 4.2.1.1

The Population Systematic Errors were 0.02, 0.04 and 0.22 cm in the ML, CC and AP directions respectively as shown in Table 4.2.1.2. The mean vector displacement for the population was 0.69 (±0.45) as shown in Table 4.2.1.1.

The Random Errors calculated in the ML, CC and AP directions were 0.21 (±0.1657), 0.30(±0.1289) and 0.30 (±0.1560) cm respectively as shown in Table 4.2.4.1

The Population Random Errors were 0.21, 0.30 and 0.30cm in the ML, CC and AP directions respectively as shown in Table 4.2.4.2. The mean vector displacement for the population was 0.6853(±0.4531) as shown in Table 4.2.4.1

The results of our study were correlating with results obtained from the other studies (3,4,5,6) and they were all within the tolerance limits of 0.5cm. Systematic Errors detected by the CBCT were more in the antereoposterior [AP] direction.

6.2.2. ON BOARD IMAGER

A study done by Adamcyzk et al on position correction strategies on patients with prostate cancer on IMRT with kV 2D-2D matching showed errors of -0.06 (± 0.47), 0.26 (± 0.38) and -0.11 (±0.54)cm in the ML, CC and AP directions respectively(35).

Studies in gynecological malignancies by Kim et al(39) showed Systematic Errors of 0.24, 0.25 and 0.10cm and Random Errors of 0.5, 0.38 and 0.4cm in the ML, CC and AP directions.

Logadottir et al in his study on accuracy of prostate localization with OBI showed Systematic Errors of 0.01, 0.007 and 0.11cm and Random Errors of 0.10, 0.12 and 0.13cm in the ML, CC and AP directions with OBI.

A study done by Zaghloul et al, to compare EPID and MV CBCT(41) in both head and neck and non head and neck patients showed the Systematic Errors with EPID were 0.16 (±0.13), 0.18 (±0.17), and 0.14 (±0.15)cm and 0.16 (±0.13), 0.23 (±0.17) and 0.24 (±0.16) cm for MV-CBCT

in the ML,CC and AP directions respectively. Random Errors with EPID were 0.14 (±0.15), 0.20 (±0.17) and 0.12 (±0.16) cm and 0.15 (±0.13), 0.19 (±0.15), and 0.21 (±0.17) cm for MV-CBCT in the ML, CC and AP directions respectively.

Systematic Errors of head and neck patients(41) had a statistically significant difference in the ML and CC directions (p value of 0.027 and 0.003 respectively), whereas in the non-head and neck patients there was a statistically significant difference only in the ML direction (p value of 0.031). In head and neck patients, the Random Errors were significantly different in the ML and CC directions, whereas in non-head and neck patients, they were significantly different in the AP direction only.

In our study, the Systematic Errors calculated for OBI ranged from 0.22 (±0.21), 0.28 (±0.21) and 0.30 (±0.45) and the Random Errors were 0.23 (±0.10), 0.28 (± 0.17) and 0.25 (± 0.17) in the ML, CC and the AP directions respectively as shown in Table 4.2.2.1 and 4.2.5.1.

The Population Systematic Error calculated for OBI was 0.05, 0.10 and 0.12 and 0.23, 0.28 and 0.25cm in the ML, CC and AP directions respectively as shown in Table 4.2.2.2 and 4.2.5.2.

The results of our study were correlating with results obtained from the other studies and they were all within the tolerance limits of 0.5cm.The errors obtained in OBI were lower as compared to CBCT.

6.2.3. COMPARISON BETWEEN CBCT AND OBI

The expected uncertainty during inter-fraction treatment in abdomen and pelvic malignancies is considered as 4.5 to 7mm according to the AAPM task group 2011(43).

A margin of 5mm is considered as the tolerance limit and an error ≥5mm is considered as error which warrants correction prior to IMRT treatment in pelvic malignancies in our Institution.

A study by Lim et al done on pelvic IMRT for carcinoma cervix patients supported that a 0.5cm CTV to PTV margin would be adequate(44).

Kim et al in their study on evaluation of set up errors using daily kilo voltage imaging arrived at a Van Herk margin of 0.7, 0.62 and 0.53cm in the ML, CC and AP directions. But as per their institutional protocol they were within the tolerance limits(39).

Bondar et al, proposed a margin of 5mm in cervical malignancies on IMRT(45).

In our study the comparison of the Systematic Errors between CBCT and OBI showed that 2 patients in the CBCT and one patient in the OBI in the ML direction [Fig 4.12], 1 patient in the CBCT and 2 patients in the OBI in the CC direction [Fig 4.13] and 5 patients in CBCT and 3 patient in OBI exceeded the tolerance of 5mm in the AP direction [Fig 4.14].

The comparison between the CBCT and the OBI Random Errors showed that 1 patient in the CBCT in the ML direction [Fig 4.26], 1 patient each in CBCT and OBI in the CC direction [Fig 4.27] and 1 patient in the CBCT in the AP direction [Fig 4.28] exceeded the tolerance of 5mm.

On comparison, the Systematic Errors in CBCT were more compared to OBI which suggests that CBCT detected more errors than OBI due to better soft tissue matching. The Random Errors were comparable between the two modalities.

The Radial Systematic Errors as shown in Fig 4.29 and 4.30 ranged from 0.18 to 1.82cm for CBCT and 0.0 to 1.31cm for OBI. The Radial Random Errors shown in Fig 4.31 and Fig 4.32 ranged from 0.27cm to 0.85 cm in CBCT and 0.24 to 0.74cm in OBI.

The mean vector displacement exceeded the tolerance limit both in CBCT and OBI, probably because 5 patients exceeded the tolerance limits of 0.5cm (0.73, 0.93, 1.80, 0.57and 0.90cm) in the AP direction in CBCT and 3 patients exceeded the tolerance limits of 0.5cm (0.60, 0.63 and 1.30]) in the AP direction in OBI.

These depict that the overall vector length was more in the Systematic Errors as compared to Random errors. CBCT has the advantage of better soft tissue visualization which helps in detecting more errors compared to OBI which detects errors based on bony anatomy only.

The Bland-Altman plot between CBCT and OBI did not show agreement between CBCT and OBI in detecting set up errors.

Snir et al in his study on IMRT of carcinoma prostate showed that the CBCT is necessary for treatment verification(46).

Palombarini et al suggested that daily kV CBCT is preferable for high dose gradient IMRT treatments like carcinoma rectum where there can be variable filling of the rectum and bladder which can lead to a geographical miss of the target(40). Another study by Kim et al comparing CBCT and OBI in gynecological malignancies showed that verification of set up errors were not statistically significant between the 2D-2D imaging and the 3D-3D imaging(39).

CBCT and OBI are two modalities which cannot be compared but when used together gives an additional advantage of both soft tissue and bony anatomy ensuring improved accuracy of treatment delivery.

6.2.4. CTV TO PTV MARGIN

The CTV to PTV margin was calculated by the 3 formulae as given in the literature (8, 9).

1. Van Herk's formula: $2.5\Sigma + 1.64\ \sigma$

2. Stroom's formula: $2\Sigma + 0.7\sigma$

3. ICRU formula: $\Sigma + 0.7\sigma$

where Σ is the Population Systematic Error and σ Population Random Error

In the study by Van Herk et al the CTV to PTV margins were calculated for CBCT and OBI. The margins calculated by the Van Herk's formula were 0.25 and 0.21, by Stroom's formula it was 0.17 and 0. 14 and by ICRU it was 0.10 and 0.08 cm for CBCT and OBI respectively (47).

The CTV to PTV margins calculated using Van Herk's formula in gynecological malignancies were found to be 0.91, 0.83 and 0.55 cm in ML, CC and AP directions according to Lim et al(39).

In our study the comparison between CBCT and OBI by Van Herk's formula showed a margin of 0.41, 0.60 and 1.04cm and 0.5, 0.7 and 0.71cm in the ML, CC and AP directions respectively. The margin calculated by Stroom's formula was 0.19, 0.23 and 0.65cm by CBCT and 0.26, 0.39 and 0.41cm by OBI in the ML, CC and AP directions respectively.

The margin calculated by the ICRU formula were 0.17, 0.25 and 0.43cm by CBCT and 0.21, 0.29 and 0.29cm by OBI in the ML, CC and AP directions respectively as shown in Table 4.4.1. In comparison with the other studies (1, 3, 5) our margins were within the limits of 0.5cm, in majority of patients as per the Institutional protocol where the CTV to PTV margin was considered as 0.5cm. The margin exceeded to a maximum of 1.04cm in the AP direction by CBCT and a maximum of 0.7cm in the CC and AP direction by the OBI.

6.2.5. TIME TRENDS

The impact of time on treatment plays an important role in determining the frequency of imaging modality to detect set up errors. The increased anxiety and rigid posture of the patient during the initial treatment causes more set up errors. These may persist for the first few treatments and as this tension is relieved and the muscles begin to relax, and the patient can have smaller displacements to any direction which have to be checked by weekly imaging. This greatly influences the set up accuracy. Checks not only at the start of the treatment are suggested but repeated checks have to be continued to ensure set up accuracy.

In our study there was a time trend seen where the errors gradually decreased in most of the patients, except during the 7^{th} week of treatment in the mediolateral direction alone.

6.2.6. LIMITATIONS OF THE STUDY

- The sample size is small to formulate an acceptable CTV to PTV margin to convert to an Institutional protocol.

- The inclusion criteria included all the patients with any pelvic malignancy on IG-IMRT, so this will only give the overall general set up errors in pelvic malignancies and not for any specific malignancy.

- The Body Mass Index (BMI) of a patient was not considered for the analysis which could have contributed to the shifts or displacements during set up.

- Inter observer variation might have influenced the Errors caused during the set up of the patient due to different personnel treating the patient on various days and that was not taken into account in this study.

6.2.7. RECOMMENDATION

- Similar studies on a larger sample size to determine the CTV to PTV margin and to standardize it for individual Institutions.
- A site specific subset analysis of the pelvic malignancies to determine the set up errors for various sites and to determine the CTV to PTV margin.eg: Prostate, Cervix
- Documentation and calculating the BMI of each patient and analyzing it as a predictor variable in the statistical analysis in further studies.

- It would be preferable to have one personnel treating the patient everyday to reduce inter observer variation and also keep the patient comfortable.

7. CONCLUSIONS

- Cone Beam Computed Tomography (CBCT) and On Board Imager (OBI) are effective tools for determining the Systematic, Random and Radial set up errors.

- Comparison of the CBCT and the OBI showed that CBCT detected more errors than the OBI in pelvic malignancies in patients on IG-IMRT due to better soft tissue detection.
  The two modalities cannot be compared with each other and cannot replace each other but have to be used symbiotically and appropriately according to the type of malignancy.

- The CTV to PTV margin followed in the Institution seemed adequate in the sample size studied though it is small. This knowledge reassures the Clinician that accurate treatment delivery is being done.

- The errors were found to be decreasing over time, as patients became comfortable and familiar with the treatment set up, showing a time trend leading to improved accuracy in set up. This again reassures that weekly imaging or even less is sufficient in the later weeks of radiotherapy.

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ANNEXURE I

Christian Medical College, Vellore

Department of Radiotherapy

An observational study to compare the OBI and CBCT in verifying the patient position during pelvic IMRT

Information sheet

You are being requested to participate in a study to verify your position during treatment by taking an OBI[a form of X-ray] and a CT scan [CBCT-cone beam CT] .There are no extra side effects except for negligible amount of radiation you will receive during the OBI. We hope to include about 30 people from this hospital in this study.

What does OBI do?

We regularly do CT scans in the first 3 days and then weekly once to check your position during treatment to make sure the treatment is delivered correctly. Now we also do an additional OBI [X-ray] to verify your position as an additional check.

Does OBI have any side effects?

OBI is a form of X-ray which has a negligible amount of radiation of about 2 Mu which will not cause any side effects

If you take part what will you have to do?

If you agree to participate in this study every day after you are positioned for treatment both OBI and CBCT will be taken to verify your position. Once ensured that your position is correct the treatment will be carried out. This will be done for the first 3 days of your treatment and then weekly once till the end of treatment.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

Will you have to pay for the OBI?

The OBI will be done at no additional cost to your regular radiotherapy expenses.

What happens after the study is over?

You will have to just complete your treatment and can be on follow up as per the advice of your oncologist.

Will your personal details be kept confidential?

The results of this study may be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

INFORMED CONSENT

Study Title: ***observational study to compare the OBI and CBCT in verifying the patient position during pelvic IMRT***

Study Number:
Participant's name:
Date of Birth / Age (in years):

I_____
_____, son/daughter/wife of _____

(Please tick boxes)
Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]
I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
I understand that my identity will not be revealed in any information released to third parties or published [ ]
I voluntarily agree to take part in this study [ ]

Name:
Signature:
Date:

Name of witness:
Relation to participant:
Date:

ANNEXURE II

CLINICAL RESEARCH FORM

- Name :
- Age:
- Sex:
- Address:
- Phone No:
- Mobile No:
- Landline No:
- Diagnosis and stage:
- Treatment: Radiation alone [ ] Chemotherapy +RT [ ]
- Dose of radiation:
- Duration of RT:
- Date of starting RT:
- Date of completion of RT:
- No: of OBIs done:
- No: CBCT done:

ANNEXURE III

SHIFT SHEET

Name: Hospital Number: Diagnosis:

Date	CBCT ML [X]	OBI ML [X]	CBCT CC [Y]	OBI CC [Y]	CBCT AP [Z]	OBI AP [Z]	

ANNEXURE IV

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Ed
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

February 20, 2012

Dr. Renitha Mirriam Cherian
PG Registrar
Department of Radiotherapy
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL**:
Comparison of Electronic Portal Imaging Device (EPID) and Cone Beam Computerized Tomography (CBCT) for position verification in pelvic malignancies on IMRT to quantify the systematic and random error.
Dr. Renitha Mirriam Cherian, PG Registrar, Radiotherapy, Dr. Selvamani. B, Dr. Subhashini John, Dr. Rajesh I, Dr. Rajesh B, Dr. Patricia, Dr. Saikat Das, Radiotherapy.

Ref: IRB Min. No. 7633 dated 3.10.2011

Dear Dr. Cherian,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Comparison of Electronic Portal Imaging Device (EPID) and Cone Beam Computerized Tomography (CBCT) for position verification in pelvic malignancies on IMRT to quantify the systematic and random error" on October 3, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Informed Consent Form (English)
3. Clinical Research Form
4. Cvs of Drs. Renitha Mirriam Cherian, Selvamani, Subhashini John, Rajesh I, Rajesh B, Patricia, Saikat Das
5. A CD containing documents 1 - 4

ANNEXURE IV

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
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Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on October 3, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

Name	Qualification	Designation	Other Affiliations
Dr. B.J.Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	Non-CMC
Mr. Harikrishnan	BL	Lawyer	Non-CMC
Mrs. Mary Johnson (on behalf of Dr. Jayarani Premkumar)	M.Sc. (Nursing), Ph.D.	Nursing Superintendent, CMC.	
Dr. Vathsala Sadan (on behalf of Mrs. Rosaline Jayakaran)	M.Sc. (Nursing), RN, RM	Dean, College of Nursing, CMC.	
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Rese CMC.	

We approve the project to be conducted as presented.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

A sum of ₹ 60,000/- (Rupees Sixty thousand only) is sanctioned for 1 ½ year.

Yours sincerely,

Dr. Alfred Job Daniel
Principal& Chairperson (Research Committee)
Institutional Review Board

Chairperson (Research Committee) &
Principal
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

ANNEXURE IV

Office of the Vice Principal (Research)

Christian Medical College
Vellore 632 002

Ref: 11/2011

February 16, 2012

The Treasurer
C.M.C.

Dear Mr. Denzil,

Sub: **FLUID Research grant project NEW PROPOSAL**:
Comparison of Electronic Portal Imaging Device (EPID) and Cone Beam Computerized Tomography (CBCT) for position verification in pelvic malignancies on IMRT to quantify the systematic and random error.
Dr. Renitha Mirriam Cherian, PG Registrar, Radiotherapy, Dr. Selvamani. B, Dr. Subhashini John, Dr. Rajesh I, Dr. Rajesh B, Dr. Patricia, Dr. Saikat Das, Radiotherapy.

Ref: IRB Min. No. 7633 dated 3.10.2011

The Institutional Review Board at its meeting held on October 3, 2011 vide Min. No 7633 accepted the project for 1 year at a total sanction of ₹ 60,000/- (Rupees Sixty thousand only). Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Dr. Renitha Mirriam Cherian and Selvamani.

Thank you.

Yours sincerely,

Dr.Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Renitha Mirriam Cherian, PG Registrar, Department of Radiotherapy, CMC
Dr. Selvamani. B, Department of Radiotherapy, CMC

ANNEXURE V
PLAGIARISM RECEIPT AND REPORT

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This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

Paper ID	384453246
Paper title	COMPARISON OF ON BOARD IMAGER [OBI] AND CONE BEAM COMPUTERISED TOMOGRAPHY [CBCT] FOR POSITION VERIFICATION IN PELVIC MALIGNANCIES ON IMAGE GATED INTENSITY MODULATED RADIOTHERAPY
Assignment title	Medical
Author	Renitha Miriam CHERIAN
E-mail	renitha_cherian@yahoo.co.in
Submission time	17-Dec-2013 12:16AM
Total words	12894

First 100 words of your submission

1. AIM OF THE STUDY 1. Comparison of On Board Imager [OBI] versus Cone Beam Computed Tomography [CBCT] in the verification of positional accuracy in pelvic malignancies in patients undergoing high precision Image gated intensity modulated radiotherapy [IG-IMRT] 2. Quantification and comparison of total, systematic and random errors in the Mediolateral [x], craniocaudal [y] and antereoposterior [z] directions to help define the clinical target volume [CTV] to planning target volume [PTV]. 3. To analyze the time trend in pelvic malignancies during Intensity Modulated Radio Therapy (IMRT) which may enable to reduce the number of Cone Beam Computed Tomography (CBCT) done in later weeks of...

COMPARISON OF ON BOARD IMAGER [OBI] AND CONE BEAM COMPUTERISED TOMOGRAPHY [CBCT] FOR POSITION VERIFICATION IN PELVIC MALIGNANCIES ON IMAGE GATED INTENSITY MODULATED RADIOTHERAPY

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