Original Article

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Role of Image Guided Radiotherapy (IGRT) in Patients Treated with Intensity Modulated Radiotherapy (IMRT) & Volumetric Modulated Arc Therapy (VMAT) in Head and Neck and Pelvic Cancers

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Abstract

Background: IGRT is the latest development for increasing the precision and accuracy in radiation therapy. Usage of specialized multi professional teams for coordinating geometric verification and use of clearly defined protocols are essential for IGRT. Reducing dose to the OARs using IMRT & VMAT and reducing the size of PTV using IGRT enables radiation dose escalation, which in turn improve the treatment outcomes. *Aims:* To evaluate set up errors in patients treated with Intensity modulated radiotherapy / Volumetric modulated arc therapy using Cone beam CT (CBCT) in head and neck and pelvic cancer sites and to study adequacy of PTV margin by applying set up errors. *Methods and Materials:* A total of thirty two patients were enrolled into the study, which included 16 Head and neck site, 16 pelvic sites that were planned with either IMRT or VMAT. CBCT was acquired for each patient on day 1, 2, 3 and thereafter every week until the completion of treatment. The CBCT images were fused with planning CT images. The PTV margin was estimated by calculating the systematic and random errors in X, Y, Z directions. *Results:* Data collected was analyzed with single sample t test. A total of 288 CBCT were taken for this study. The systematic and random errors were calculated in both head and neck and pelvis 16 patients each. The systematic error for H&N site in cranio caudal (CC), medio lateral(ML), anteroposterior (AP) were 0.2cm, 0.2 cm, 0.2 cm respectively. The random errors in H&N sites patients in CC, ML, and AP were 0.2 cm, 0.2cm, 0.2 cm respectively. The PTV margin for H&N site in CC, ML, AP were 0.7cm, 0.5cm, 0.5cm respectively. For pelvic site, the systematic error in CC, ML, AP were 0.3 cm, 0.2 cm, 0.2cm respectively, where as the random errors were 0.2 cm, 0.3cm, 0.2 cm respectively in the same direction. The estimated PTV margin for pelvic site in CC, ML, AP were 0.8cm, 1.0cm, 0.7cm respectively. *Conclusion:* For H & N and pelvic sites, treated with IMRT/VMAT the PTV margin of 5mm is not sufficient. Hence treatment verification with IGRT is very crucial to identify and correct the set up errors in order to deliver the planned treatment.

Keywords: Image Guided Radiotherapy (IGRT); Intensity Modulated Radiotherapy (IMRT); Volumetric Modulated Arc Therapy (VMAT).

Introduction

IGRT- Image guided radiotherapy is the latest technique in the field of radiotherapy. Goal of the IGRT process is to improve the accuracy of the radiation field placement, and to reduce the exposure of healthy tissue during radiation treatments. IMRT is a precise and safe delivering process which minimizes the radiation to the surrounding normal tissues and gives more appropriate treatment with minimal toxicities. Volumetric modulated arc therapy (VMAT) is a novel radiation technique which can achieve highly conformal dose distributions with improved target volume coverage and sparing of normal tissues compared with conventional radiotherapy techniques.

The introduction of modern radiation techniques such as IMRT /VMAT has been complicated by the substantial changes in position and shape of the target volume that occur during the course of the treatment. Slight geometrical deviation can result in under dosing part of the target volume and overdosing the surrounding critical normal tissues. The development of advanced three-dimensional radiotherapy

techniques has emphasized the importance of accurate target volume localization. IMRT can produce dose distributions that conform very precisely to a concave volume, sparing surrounding structures and reducing normal tissue toxicity. However, with the steep dose gradients, there is a potential risk of a geographical miss. In IGRT role of verification has much importance in daily treatment process. Geometric verification is mandatory for all megavoltage external beam radiotherapy and carried out within a clearly defined structure with institutional protocols. In ensuring the right radiation dose delivery to the right place, 2 measures are needed Geometric verification and Dosimetric verification.

Aim of geometric verification is to ensure that the geometric accuracy of radiotherapy delivered is within the limits set by uncertainty margin allowed in the treatment plan. Verification is a process by which accuracy of radiotherapy is achieved.

Pretreatment verification is the process that compares the reference images with the planned treatment before the course of radiotherapy. IGRT is a radiotherapy process which uses images which is obtained during treatment delivery and intervention to correct set up before delivery. Despite improved imaging it is not possible to correct for all components of geometric error in radiotherapy. These include inevitable residual errors which may arise due to target delineation uncertainty and movement of patient or internal organs. Set up error is used to describe the discrepancy between intended and actual treatment position. It comprises both systematic and random component. A gross error is unacceptably large setup error that could under dose the part of CTV& PTV and overdose a organ at risk (OAR). Our aim is to evaluate set up errors in patients treated with IMRT/VMAT in head & neck and pelvis cancer sites and to check the adequacy of PTV margin for head & neck and pelvis cancer sites by applying the set up errors.

Materials and Methods

Thirty two patients with histological proven H&N and pelvic malignancies planned for definitive or adjuvant radiotherapy with or without chemotherapy from January 2015 to January 2016 were included in the study after obtaining the ethical committee approval.

Sample Size

The sample size has been estimated in consultation with a bio-statistician. The sample size chosen is 32. This was estimated based on previous year hospital records.

Inclusion Criteria

- Patients of Head and neck cancer treated with IMRT and VMAT
- Patients with pelvic cancer sites treated with IMRT and VMAT.

Exclusion Criteria

- Patients treated with 3DCRT and conventional RT.
- Patients taken for re simulation, because of weight loss etc.

Method

Estimated sample size was thirty two and 16 patients among them were Head and Neck Carcinomas and 16 patients were pelvic carcinomas. IMRT or VMAT plans are generated and treated. A total of 32 patients were enrolled into this study. A total of 32 IMRT or VMAT plans were generated for them.

All patients were treated as per IMRT or VMAT plans are generated. IMRT or VMAT plans were used for study purpose only. For pelvis cases a thorough clinical history, gynecological examination was performed. A punch biopsy was taken from lesion. Baseline investigations including complete blood count, renal function tests, liver function tests, HIV & Hbs-Ag were done. All patients underwent Chest X ray, MRI abdomen pelvis with contrast done to delineate the gross disease. Patients were staged as per the FIGO / AJCC 7th edition 2010.

For Head and Neck cases a thorough clinical history, physical examination, local examination, IDL, Fibreopticscopy was performed. A punch biopsy was taken from lesion. Baseline investigations including complete blood count, renal function tests, liver function tests, HIV & Hbs-Ag were done. All patients underwent Chest x Ray, CECT Head and Neck with contrast/MRI done to delineate the gross disease. Patients were staged as per the AJCC 7th edition 2010.

External Beam Radiotherapy Planning Steps

Patient preparation (for Pelvis patients only) – Bowel and bladder preparations were done before simulation. Patients were advised to take laxatives previous night and to properly empty bowels. All were

asked to drink 500 ml of water half hour before simulation.

Immobilization & CT Simulation

Pelvis: Patients were positioned and immobilized with pelvic 4 clamp thermoplastic mould. Three fiducial markers were used as reference marks and to define isocentre using lasers.

H&N: Patients were positioned and immobilised with H&N 4 clamp thermoplastic mould with shoulder retractor. Three fiducial markers were used as reference marks and to define isocentre using lasers.

Radiotherapy planning scan was performed on GE Helical CT after meeting all the protocol requirement with 2.5 mm slice thickness. A unique Radiotherapy serial no was assigned to each patient (RT NO).

Scanned images were imported to planning system Eclipse 7.1.

The volumes were contoured for all pelvis and H&N sites as per the consensus contouring guidelines.

Treatment Verification Protocol

Patients were positioned on the treatment couch using immobilization mask by aligning lasers on the marked isocenters, the same simulation parameters were reproduced. Isocenter shift if any was applied. All 32 patients underwent a Cone Beam CT (CBCT) on day1, day 2, day 3, and there after weekly until the completion of treatment with VARIAN On Board Imaging. The shifts were calculated in x,y,z direction. No rotational errors were accounted. Tolerance limit was kept as 3mm in any direction. If the shift was >3mm then the patient was repositioned and repeat imaging was done. If the shift persist for >3mm then it was corrected but not applied. The average of 3 days of shifts was calculated for all directions and new isocenter was freezed. This isocenter was used for daily treatment. The shifts on day 1, day 2, day 3 were used to calculate systematic error. The CBCT imaging was repeated every week. The significant shifts in x,y,z direction were corrected for that particular day. The mean of these shifts were calculated as random error.

After evaluating systematic errors and random errors PTV_{margin} is calculated by using the following formulas.

Statistical Analysis

Data collected was analyzed with single sample t test. Single sample t test was used to analyze the data. For H & N and pelvic sites, treated with IMRT/ VMAT the PTV margin of 5mm is not sufficient and more significant in cranio caudal direction in H&N and medio lateral direction in pelvis.

Results

Head & Neck

A total of 150 CBCT were taken for 16 patients and set-up errors, both systematic and random errors were calculated in 3 dimensions. PTV margin is calculated by using both systematic and random error in 3 dimensions. Errors in 3 dimensions were taken on day 1, day 2, day 3, shifts in a particular direction were applied and corrected on the same day.

Systematic Error is taken as a MEAN of day 1, day 2, day 3.

Random Error is taken as MEAN of week (1-7).

Set-up error (systematic and random) in X, Y, Z directions and PTV margin using Van Herks Model for 16 Head & Neck Patients. (Table 1,2 and Figure 1).

Pelvis

A total of 128 CBCT were taken for 16 patients and set-up errors, both systematic and random errors were calculated in 3 dimensions. PTV margin is calculated by using both systematic and random error in 3 dimensions. Errors in 3 dimensions were taken on day 1, day 2, day 3, shifts in a particular direction were applied and corrected on the same day.Systematic Error is taken as a MEAN of day 1, day 2, day 3. Random Error is taken as MEAN of week (1-5). Set-up error (systematic and random) in X, Y, Z directions and PTV margin using Van Herks Model in 16 Pelvis Patients. (Table 3,4 and Figure 2).

Table 1: Set-up errors and PTV margin values obtained for 16 Head & Neck Patients in all 3 directions

	x-axis Medio-lateral (cm)	y-axis anterio-posterior (cm)	z-axis craniocaudal (cm)
SE	0.2	0.2	0.2
RE	0.2	0.2	0.2
PTV margin	0.5	0.5	0.7

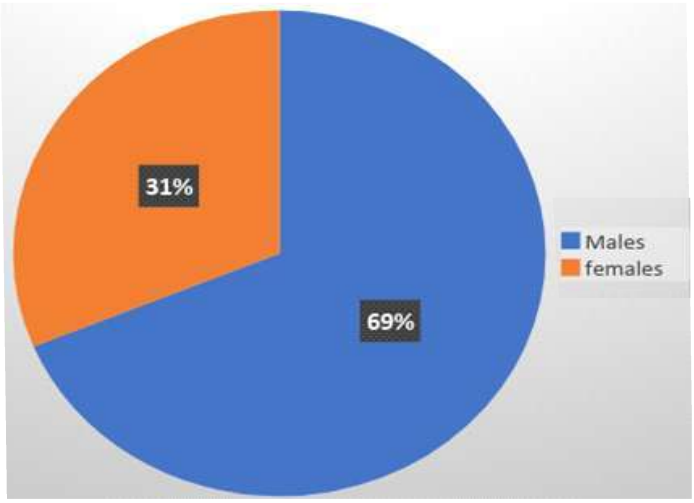

Fig. 1: Gender wise distribution in study

Table 2: Site and stage wise distribution of cases in Head & Neck site

Site	No. of patients	Percentage%
Oropharynx	4	25
Oral cavity	7	44
Nasopharynx	1	6
Larynx	4	25
Total	16	100
Stage		
Stage I	-	
Stage II	5	31
Stage III	6	48
Stage IV	5	31
Total	16	100

Table 3: Set-up errors and PTV margin values obtained for 16 Pelvic Patients in all 3 directions

	x-axis Medio-lateral (cm)	y-axis anterio-posterior (cm)	z-axis craniocaudal (cm)
SE	0.3	0.2	0.3
RE	0.3	0.2	0.2
PTV margin	1	0.7	0.8

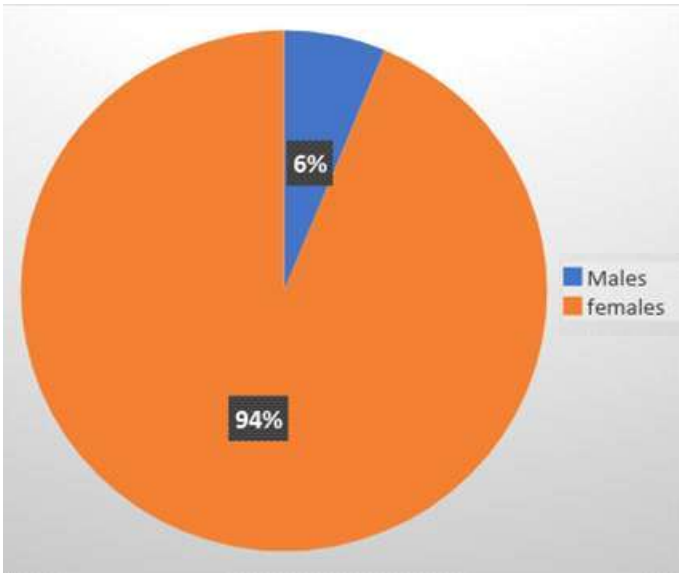

Fig. 2: Sex wise distribution of cases in Pelvic site

Table 4: Site and stage wise distribution of cases in Pelvic sites

Site	No. of Patients	Percentage (%)
Cervix	14	88
Anus	1	6
Rectum	1	6
Total	16	100
Sage		
Cervix Figo IB2	1	6
Cervix Figo II	7	45
Cervix Figo III	5	31
Cervix Figo IV	1	6
Anus Stage III	1	6
Rectum Stage III	1	6
Total	16	100

Discussion

The treatment effects of patient set-up errors are more pronounced in IMRT planning because of the high dose gradients obtained to spare organs at risk that are adjacent to the target volume. The purpose of the current study is to evaluate set-up errors and subsequently to decide on the appropriate PTV margin definition for the IMRT treatments in our department.

We applied an on-line protocol for 16 patients with different sites of H&N like oral cavity, oro pharynx, hypo pharynx and nasopharynx. Security on daily patient's positioning is usually based on the immobilization mask, that it may be different with the position of the internal anatomy.

Two classes of set-up uncertainties are identified; systematic and random. Systematic error is the deviation between the planned patient position and the average patient position over the whole course of radiation therapy, and machine related errors and target delineation uncertainties are part of this systematic errors. The random error is the day to day deviation from the average target position introduced with internal motion, and it reflects the patients related or mask related factors. The range of shifts in CC, ML, AP were -0.3cm to 0.3cm, -0.33cm to 0.13cm, -0.3 to 0.16 respectively.

We analyzed errors according to random and systematic set-up errors. In our study, we found that the systematic errors and random errors in CC, ML and AP were respectively 2.15, 1.59, 1.60 and 1.79, 1.92, 1.50 in mm. These systematic errors could be due to the precision on the lasers alignment either of the simulator or of the treatment unit oßr a systematic error of the observer, or of the set-up.

Suzuki et al. [4] published a study in which the mean of the systematic set-up errors for all directions ranged within 1 mm, the average of the individual random set-up errors ranged from 0.7 to 1.6 mm. In our study the mean of systematic set-up errors in CC, ML, and AP ranged from 0 to 3.6, 0 to 1.1 and 0 to 0.9 in mm respectively. The mean of random set-up errors in CC, ML and AP ranged from 0 to 3.33 mm in all directions.

Inter fractional set-up errors evaluation by daily electronic portal imaging of IMRT in head and neck cancer patients a study done by Berrin Pehlivan et al. [5] had included 20 head and neck patients and daily portal imaging was done, systematic errors and random errors were evaluated to calculate PTV margin. For the 20 patients 567 images were taken and standard deviation in three directions were calculated obtaining a systematic error of less than 1 mm and random error of 2 mm with 3-4 mm of PTV margin in 3 directions which was significant only in cranial caudal direction. Set-up error increased significantly when the scenario of one portal imaging every 3 fractions was adopted. Portal imaging in AP and ML direction once 2 days a week and every 2 days in the CC direction would be adequate to overcome the problem of set-up errors.

Verification of setup errors in external beam radiation therapy using electronic portal imaging done by Krishna murthy et. al. [7] objective of this study was to conduct an audit on QA aspects of treatment delivery by the verification of the treatment fields; position on different days to document the efficiency of immobilization methods and reproducibility of treatment, 20 patients treated for head and neck and pelvis each. Portal images acquired using the EPID systems attached to the Varian linear accelerators were superimposed on the reference images.

Borut Krageli [7] observed that setup errors in positioning the patients influence the size of safety margin and thereby also the size of irradiation field

and toxicity of radiotherapy. In this study 23 carcinoma prostate patients were taken and 95 images were done, systematic and random errors were evaluated and safety margin for adequate CTV coverage was calculated. The safety margin determining the planned target volume (PTV) was 1.5 cm wide; in the closing phase of radiotherapy, in which only the prostate was exposed to irradiation, the safety margin was reduced to 1 cm, and on the dorsal side, to 0.7 cm.

Zelefsky [8], in the patient in prone position and at a safety margins of 1cm in the anterior lateral and cranial caudal directions and of 0.6 cm at the dorsal side, the coverage of CTV at the dorsal side is 85% before and 96% after the corrections for setup error and prostate displacement. The 90% probability of CTV coverage of the irradiation field at the safety margin of 1 cm along the lateral axis is achieved in 91% of patients, and in cranial and caudal directions in 91% and 87% of patients, respectively, and on the anterior and posterior side in 96% and 78% of patients, respectively on side. By reducing the dorsal margin to 0.7 cm, the 90% probability of CTV involvement in the irradiation field would be obtained only in 74% of patients [7].

Nath et al. [9] concluded that IGRT provides increased tumor localization by improving the identification of areas of tumor burden, by minimizing the effects of patient setup errors caused by intra/inter fraction motion, and by allowing for adaptive re-planning to changes that occur in the tumor or patient during long courses of radiotherapy. But, there is still no existing level I evidence demonstrating the benefit of IGRT over standard radio therapeutic modalities.

It is generally accepted that systematic set-up errors influence more the physical dose distribution than the random set-up errors. In the majority of the studies, systematic errors were usually larger than random errors [10,11]. Systematic errors are treatment preparation errors and influence all fractions therefore much more important in determining the margins than random errors. Random errors are treatment execution errors influence each fraction individually.

PTV margins are between 5 to 6 mm in all three directions. Based on these results we can conclude that a 5-6 mm PTV margin can be enough for adequate dose distribution in IMRT, and that this margin could be reduced to 5 mm if daily verifications are made.

The standard deviation of systematic and random errors in CC, ML, SI directions are 0.7, 0.6. 0.4mm respectively.

We applied an on-line protocol for 16 patients with different sites of Pelvis like cervix, rectum and anus. In our study, we found that the systematic errors and random errors in CC, ML and AP were respectively 2.83, 3.44, 2.37 and 1.93, 3.20, 1.83 in mm. The range of shifts in CC, ML, AP were -0.3cm to +0.4cm, -0.5 to +0.5, -0.2 to +0.4 respectively.

In our study the mean of systematic set-up errors in CC, ML, and AP ranged from 0 to 2.2, 0 to 4.3 and 0 to 3.3 in mm respectively. The mean of random set-up errors in CC, ML and AP ranged from 0.4 to 4.33, 1.0 to 6.4 and 0.4 to 4.0 in mm respectively.

PTV margins are between 7 to 10 mm in all three directions.

IGRT is the latest development for increasing the precision and accuracy in radiation therapy. Usage of specialized multi professional teams for coordinating geometric verification and use of clearly defined protocols are essential for IGRT. Main objective of this study was to evaluate set up errors in patients treated with Intensity modulated radiotherapy / Volumetric modulated arc therapy using CBCT in head and neck and pelvic cancer sites to study adequacy of PTV margin by applying set up errors. For H & N and pelvic sites, treated with IMRT/VMAT the PTV margin of 5mm is not sufficient. Hence treatment verification with IGRT is very crucial to identify and correct the set up errors in order to deliver the planned treatment.

Conclusion

Role of imaging to be done in patients treated with IMRT/VMAT which if done in the starting few days of the treatment will avoid systematic error , and imaging done every week of the treatment will avoid random error. For head and neck carcinomas significant PTV margin is obtained in cranio caudal direction and for pelvis in medio lateral direction.

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