Investigation of geometrical, clinical uncertainty and dosimetric studies in 3D interstitial brachytherapy of radical breast implants

By

RITU RAJ UPRETI

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Annexure 1

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Name: Dr. D.D. Deshpande
Designation: Professor HBNI;
Department/Centre: Medical Physics/Tata Memorial Hospital
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List of Publications arising from the thesis

Journal

1. "Interobserver variation of target volume delineation and its impact on irradiated volume in accelerated partial breast irradiation with intraoperative breast implant". **Upreti RR**, Budrukkar A, Wadasadawala T, Misra S, Gurram L, Pathak R, Deshpande D D. Journal of Contemporary Brachytherapy. 2017; 9(2): 139-145.
2. "Change of target volume and its dosimetric impact during the course of accelerated partial breast irradiation (APBI) using intraoperative multicatheter interstitial brachytherapy after open cavity surgery". **Upreti RR**, Budrukkar A, Upreti U, Misra S, Wadasadawala T, Kohle S, Deshpande D D. Brachytherapy. 2017; 16(5):1027-1034.
3. "Impact of inter-observer variations in target volume delineation on dose volume indices for accelerated partial breast irradiation with multi-catheter interstitial brachytherapy". **Upreti RR**, Budrukkar A, Upreti U , Wadasadawala T, Misra S, Gurram L, Pathak R, Deshpande D D. Radiotherapy and Oncology. 2018; 129:173-179.

Conferences

1. Interobserver variation in delineating lumpectomy cavity and CTV for patient undergoing APBI using intraoperative implant and its impact

on implant dosimetry. **Upreti RR**, Budrukkar A, Wadasadawala T, Misra S, Gurram L, Pathak R, Deshpande D D. Physica Medica, 2016; Volume 32, S3, 264. European Congress of Medical Physics (ECMP 2016) at Athens, Greece - Oral presentation.

2. "Interfraction variation in the target volume for accelerated partial breast irradiation (APBI) using intraoperative multicatheter interstitial brachytherapy and its dosimetric impact". **Upreti RR**, Budrukkar A, Upreti U, Misra S, Wadasadawala T, Deshpande D D. International conference on advances in radiation oncology (ICARO2), 20th - 23rd June 2017, IAEA, Vienna (Austria) – Oral presentation

Others publications of the student in Refereed Journals related to present work

1. "Impact of adjuvant systemic chemotherapy on wound healing and cosmetic outcome in 224 women treated with accelerated partial breast irradiation using interstitial brachytherapy. Brachytherapy". Budrukkar A, Pandit P, Wadasadawala T, **Upreti RR**, Jalali R, Gupta S, Shet T, Parmar V, Badwe R, Sarin R. 2017;16(5):935-942.
2. "Clinical outcomes of prospectively treated 140 women with early stage breast cancer using accelerated partial breast irradiation with 3 dimensional computerized tomography based brachytherapy".

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3. "Fat necrosis in women with early-stage breast cancer treated with accelerated partial breast irradiation (APBI) using interstitial brachytherapy". Budrukkar A, Jagtap V, Kembhavi S, Munshi A, Jalali R, Seth T, Parmar V, **Upreti RR**, Badwe R, Sarin R. Radiother Oncol. 2012; 103 (2):161-5.

Ritu Raj Upreti

DEDICATIONS

My family, friends, colleagues and all well wishers

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Ritu Raj Upreti

CONTENTS

Abstract:

Introduction of volumetric imaging in brachytherapy during the last decade witnessed the transition from conventional brachytherapy to CT based three dimensional (3D) conformal brachytherapy. Active source positions in the vicinity of the target volume, steep dose gradients and rapid dose fall off demands the overall accuracy in 3D conformal brachytherapy more stringent. Since brachytherapy is subject to various uncertainties, it is necessary to identify these uncertainties, their magnitude, and dosimetric impact for each treatment site and technique. Aim of this thesis was to investigate the uncertainties in CT image based 3D conformal interstitial breast partial breast brachytherapy implants, which have not been adequately addressed so far in the literature.

The major findings of this thesis are as follows:

The reconstruction n error leads to geometrical uncertainties, which can be reduced by selection of smaller slice thickness and increasing the implant orientation from imaging plane. Significant inter-observer variation in the target delineation was found, which was significantly related to visualization of lumpectomy cavity. Excellent visualization yielded smaller variability in the target delineation. Target delineation variability showed an impact on source position along catheters. Significant impact on dose volume indices, such as decrease in coverage and conformality was found due to inter-observer variation in target delineation. Post-operative changes during the immediate post-op period after lumpectomy and catheter placement resulted in the change of target volume during partial breast brachytherapy treatment. These changes were found patient specific and showed significant reduction in the dosimetric coverage and conformality of the target volume.

Synopsis:

Last decade witnessed transition from conventional brachytherapy to three dimensional (3D) conformal brachytherapy. Conventional treatment planning utilizes set of radiograph which lacks the 3D anatomical information and resulted in larger irradiated volume. The advantages of 3D brachytherapy is to deliver conformal dose to a three dimensional target volume defined on computed tomography (CT) images and to limit the doses to surrounding healthy tissues and organ at risk (OAR). Brachytherapy allows the escalation of radiation dose with high conformality as the radiation is delivered from the inside out with a sharp fall off dose to nearby tissues. Therefore errors are less forgiving and having greater impact in brachytherapy.

The process of brachytherapy is subject to uncertainties, which includes source calibration, imaging, contouring, catheter reconstruction, dose calculations, dose delivery and anatomical variations. Investigation of these uncertainties is essential, which need to be evaluated for each treatment site and treatment techniques to estimate their impact on delivered dose to the patient.

Review of literature revealed extensive studies addressing uncertainties mainly for gynaecological, prostate brachytherapy and balloon brachytherapy for accelerated partial breast irradiation (APBI). There have been so far very limited data published for uncertainty related to 3D image based interstitial breast implants. Objectives of the work undertaken for the thesis is to investigate the uncertainties in CT image based 3D interstitial brachytherapy of multi catheter interstitial breast implants for APBI which are as follows:

a) Reconstruction errors of the catheters for interstitial breast implant using indigenously designed breast phantom
b) Inter-observer variation in the delineation of target volume
c) Dosimetric impact of inter-observer variation in target delineation
d) Change in target volume during course of brachytherapy treatment

Chapter 1: Introduction and review of literature

This chapter introduces the various treatment modalities of breast cancer treatment, breast conservation therapy (BCT), rationale of partial breast irradiation and various accelerated partial breast techniques practiced worldwide. BCT is the preferred treatment for the early stage breast cancer. APBI is a technique which irradiates the lumpectomy bed with smaller margin, instead of whole breast. In APBI higher dose can be delivered in a shorter time due to limited volume of treatment. Multi-catheter interstitial brachytherapy for APBI is one of the established techniques with long term follow-up. Brachytherapy places radioactive sources either within tumor or in close contact with the tumor volume. Dosimetric outcome of conventional brachytherapy planning is being evaluated by visualizing the isodoses qualitatively in the orthogonal planes of implant geometry. Dosimetric system used for conventional planning lacks in providing 3D relationship between the isodose volume and the anatomical boundaries of the target due to use of orthogonal radiographs. Thus the clinical realistic evaluation of the dosimetric parameters was not possible with conventional brachytherapy planning. Transition from conventional brachytherapy to three dimensional (3D) conformal brachytherapy is being witnessed in last decade. The 3D brachytherapy delivers conformal dose to a three dimensional target volume

defined on computed tomography (CT) images and limits the doses to surrounding healthy tissues and organ at risk (OAR).

Uncertainties in 3D image based external beam radiotherapy have been investigated in details and reported in literature. Uncertainties in brachytherapy were initially considered negligible based on the observation that the catheters; tumor and surrounding tissues represent a stable system. However, uncertainties in brachytherapy can lead to potential source of errors as the dose gradient is significant beyond the target volume. Review of literature revealed studies addressing the uncertainties in mainly for gynaecological and prostate brachytherapy. There have been so far very limited data published for uncertainty related to 3D image based brachytherapy using multi catheter interstitial breast implants. The work in this thesis is carried out to investigate the uncertainties in the CT image based multi-catheter interstitial breast brachytherapy (MIB).

Chapter 2: Geometrical uncertainties: Reconstruction errors:

Source localization accuracy during the CT based 3D brachytherapy treatment planning relies on the accuracy in the reconstruction of the catheters. A catheter reconstruction error in the 3D breast treatment planning is a source of uncertainty and depends on the thickness of acquired axial CT slice and the orientation of the catheters with respect to the imaging plane. Limited work is published demonstrating the reconstruction accuracy for a breast implant.

The indigenous 3D multi-slice breast phantom was designed and fabricated using PMMA sheets and implant geometry was simulated. To investigate the reconstruction errors due to rotation of implanted catheters with respect to imaging

plane a rotating platform was fabricated. Phantom was scanned with various slice thickness (0.6 mm, 2.5 mm and 5.0 mm) and rotated to different angles (0^0, 5^0, 10^0, 20^0 and 90^0). Minimum slice thickness (0.6 mm) with perpendicular orientation (90^0) from the scanning plane was taken as reference scan. Catheters were reconstructed and source was loaded to consistent dwell positions in all planning dataset. Source coordinates of reference scan was taken as reference for comparison. Coordinate transformation was performed to source coordinates for all other scans to reference scan and source coordinates was compared with the reference scan. The mean geometrical distance and standard deviation (SD) between corresponding source positions from reference data set was estimated for investigating reconstruction errors.

The mean geometrical distance and SD tends to decrease with increasing the angle between the imaging plane and catheter plane, however it increases with slice thickness. For 20^0 angular orientations of implanted tubes from imaging plane and 0.6 mm slice thickness, the least reconstruction error (SD) of 0.3 mm was observed, however the largest error (SD) of 0.9 mm was observed for 5 mm slice thickness and parallel orientation of implant. The largest mean geometric distance of 1.7 mm between corresponding source position was observed for 5 mm slice thickness and parallel orientation. Smallest slice thickness found to have least uncertainties for all implant orientations.

Chapter 3: Inter-observer variation in target volume delineation

Delineation of the structures is the weakest link in the process of radiation therapy. Inaccuracy in the delineation may result in the geographic miss and excessive irradiation of surrounding normal tissues which may have an impact on clinical

outcomes. This work was carried out to investigate inter-observer variation in target delineation in MIB for breast cancers.

To investigate inter-observer variability in target delineation, 20 retrospective patients having early breast cancer treated using partial breast brachytherpay were included for the study. Intra-operative placement of the flexible nylon catheters was performed immediately after breast conserving surgery using open cavity technique. Five radio-opaque markers were kept at the edges and the centre of lumpectomy cavity. Five radiation oncologists delineated the lumpectomy cavity (LC) and CTV on computed tomography (CT) scans. Delineation process was standardized and Cavity Visualization Index (CVI), was developed which ranges from (0 = poor) to (3 = excellent). Each patient was assigned CVI by all observers. Spatial concordance (CI_{common} and CI_{gen}), average shift in the center of mass (COM) and V_{max}/V_{min} of LC and CTV volumes were evaluated among all observers for 200 delineated contours. Relative SD (SD/mean) of LC and CTV volumes were also computed.

The mean±SD CI_{common} and CI_{gen} for LC were 0.54±0.09 and 0.74±0.06 however respective values of CTV were 0.58±0.08 and 0.76±0.05. Significant increase in Conformity Index (CI) and COM shift and decrease in V_{max}/V_{min} was observed with CVI. Cases having excellent visualization showed the least shift in median COM of LC and CTV. The mean relative SD (in %) of LC and CTV was 10.9% and 11.7% respectively. The study concluded a significant inter-observer variation in target delineation which was found larger for poorer visualized lumpectomy cavity.

Chapter 4: Dosimetric impact of inter-observer variation in target volume deleneation

Delineation variability among observers is a potential source of uncertainty in radiotherapy. Target delineation variability likely to have a dosimetric impact as the rapid dose fall exists in 3D brachytherapy. Literature review revealed that there is no published data on the impact of inter-observer variability of target delineation on implant dosimetry for MIB of breast cancer.

CTV delineation in 20 breast cancer patients treated using MIB of breast was carried out by five radiation oncologists. Graphically optimized treatment plans were generated for CTV of all observes for each patient. Dosimetric evaluation was carried out using coverage index (CI), external volume index (EI), overdose volume index (OI) and conformal index (COIN). Evaluation of other dosimetric parameters was carried out. These parameters included variation in active source positions (with step size of 0.5 cm) for each catheter and volume of prescription dose (V_{100}). The CTV coverage with common (V_{100_common}) and paired (V_{100_pair}) volume of prescription dose. In addition, relative SD (SD/mean) of CI and COIN was also computed to estimate dosimetric uncertainty of inter-observer target delineations.

The maximum variations ($\rho<0.05$) of 10.6%,10.6%, 72.7% 11.4% was found in the mean CI, OI, EI and COIN respectively when a plan is optimized to a particular delineated CTV volume of an observer and then evaluated to all other volumes to analyze dosimetry. The mean (SD) of V_{100} was 160.7 (52.1) cm^3. The coverage of CTV with V_{100_common} and V_{100_pair} was found to be 73.1 (8.1) % and 77.9 (7.3) % respectively. The maximum mean relative SD (in %) of CI and COIN was 5.7% and 7.1% respectively. The finding of the work concluded a significant dosimetric impact

of <12% in coverage and conformity of the target volume due to of inter-observer delineation variability. It was also observed that the prescribed dose to be increased to compensate the decline in target coverage due to inter-observer variation at the cost of DHI for CTV <180cm^3.

Chapter 5: Change in target volume during course of brachytherapy treatment

Intra-operative placement of catheter after open cavity surgery for breast conservation therapy leads to seroma formation and regression during the immediate post-op period as the duration of interstitial implant in situ is generally 7 – 10 days and may cause the changes in the target volume during partial breast brachytherapy. This study was carried out to investigate the target volume variability during APBI with multicatheter interstitial brachytherapy.

The change in target volumes during partial breast brachytherapy treatment was evaluated in 22 patients by acquiring CT scans for planning (CT1) and prior to last fraction (CT2). The LC and CTV were delineated in both the CT datasets by a single observer Optimized treatment plan was P_{CT1} generated on CT1 for 3.4 Gy per fraction using Ir-192 HDR source. Total 10 fractions were delivered with two fractions daily. Median time between CT1 and CT2 was 9 days. The information regarding source active positions, each position dwell times along with source activity of the P_{CT1} were manually entered in the CT2 and named as P_{CT2}. Plans were compared using CI, DHI, EI, OI and COIN.

Nine patients showed increase in CTV volume by ≥10% however decrease of ≥10% was found in 5 patients. Mean absolute difference of 13.2 % in CTV was observed when analyzed pair wise for each cases. CI and COIN was found to be

decreased by 8.4% and 5.5% for those cases showed increase in CTV volume. Decrease in CTV showed significant decrease of 13.5% in COIN which was due to increase in EI by 45%. Overall 22 cases showed significant pair wise absolute difference of 7.0±4.5% and 8.5±6.2 % in CI and COIN respectively. The work concluded that the changes in CTV volume during the partial breast brachytherapy is patient specific and need to be evaluated for every patient in the mid of the treatment.

Chapter 6: Summary, Conclusion and future directions:

6.1 Summary and Conclusion:

In this thesis the uncertainty for 3D conformal brachytherapy specific to multicatheter interstitial breast implants was investigated. The summary of the results is as follows:

The reconstruction errors lead to the geometrical uncertainty which was found to be larger when the implant and catheter orientation are near to parallel with imaging plane. As the slice thickness decreases and angle of implanted catheters with respect to imaging plane increases, there was reduction in the uncertainties. Smallest slice thickness had the least reconstruction uncertainty.

APBI using radical breast brachytherapy involves the irradiation limited to partial breast volume, which necessitates the accurate target delineation. As the volume around tumor bed is at higher risk of tumor relapse if treatment is not adequate. Present work in the thesis found a significant delineation variability in LC and CTV intra-operative multi-catheter partial breast brachytherapy, which was significantly related to cavity visualization index (CVI). The relative standard deviation in target volume delineation for intra-operative MIB was found to be 11.7%

(k=1). Patients having excellent visualization of lumpectomy cavity showed smaller delineation variability in CTV and lumpectomy cavity.

An inter-observer variation in the target delineation yielded the variations on the active dwell positions in catheters and therefore significant impact was observed on dosimetric indices. Conformal brachytherapy plans showed variations of up to 12 % in the mean dosimetric coverage and conformality of CTV. Delineation variability also yielded the CTV coverage with 73.1% with common prescription dose and 77.9% with paired prescription dose among all observers. The mean RSD of 5.7% and 7.1% (k=1) in the dosimetric coverage and conformality respectively was found due to inter-observer delineation variability.

The post-operative changes in the tumour bed after intra-operative placement of brachytherapy catheters are due to accumulation of seroma during breast conservation therapy. These temporal changes caused the patient specific variation in the CTV during APBI using multi-catheter partial breast brachytherapy and yielded a significant reduction of 5.8% in mean target coverage and 8.1% in mean conformity.

6.2 Future directions:

The present work showed that geometrical uncertainties can be minimizes by reducing scan thickness and increasing the orientation angle of the implant from imaging plane. The dosimetric impact of reconstruction errors could be a subject of investigation. Also the presence of breathing motion also has an impact on reconstruction errors and can be further investigated.

The work carried out in the present thesis showed that even though the delineation process is standardized, there is a need of further investigation for

minimizing the delineation uncertainty in those patients who has poor visibility of lumpectomy cavity. Role of other imaging modalities such as magnetic resonance imaging (MRI) and utrasonography (USG) could be a subject of investigation for the further improvements in delineation process. Few investigators reported superior consistency in target delineation and improvement in delineation variability when MRI imaging are added with CT and patients with dense breast parenchyma showed better visualization with USG imaging.

It was demonstrated that although increase in the prescription dose may be used to compensate for delineation variability for smaller target volumes ($<180cm^3$) at the cost of homogeneity for 3D conformal plans, however investigation of possibility of margins to address dosimetric variation due to target delineation variability could be a subject of investigation. Although margins in the radial directions of the catheters are not recommended in brachytherapy, margins along the catheters still can be applied.

The work in thesis demonstrated the patient specific variability in the CTV during APBI using MIB which was found to have significant impact on target coverage and conformality. Adaptive brachytherapy could be a subject of future research if the change in the target volume is larger than the intra-observer variability in target delineation.

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Glossary

3D	Three dimensional
AAPM	American Association of Physicists in Medicine
APBI	Accelerated partial breast irradiation
COIN	Conformity index
COM	Centre of mass
CT	Computerized tomography
CTV	Clinical target volume
CVI	Cavity visualization index
D95	Dose to 95% of CTV volume
D90	Dose to 90% of CTV volume
DVH	Dose volume histogram
DVI	Dose volume indices
DHI	Dose homogeneity index
EI	External volume index
GEC ESTRO	European Group of Curietherapie and the European Society for Radiology and Oncology

HDR	High dose rate
LC	Lumpectomy cavity
OAR	Organs at risk
OI	Overdose volume index
MIB	Multi-catheter interstitial brachytherapy
MLB	Multilumen balloon brachytherapy
PQI	Plan quality index
PTV	Planning target volume
RCV	Relative CTV volume
RTOG	Radiation therapy oncology group
SD	Standard deviation
TPS	Treatment planning system
TRAK	Total reference air kerma
V100	Percentage of volume receiving 100% of the dose
V_{100_common}	common volume of prescription dose
V_{100_pair}	common volume of prescription dose for respective pair

Chapter 1

Introduction

1.1 Treatment of breast cancer:

Breast cancer is the second most common cause of mortality and the most common cancer among women worldwide [1]. In last many decades, cervical cancer was the most common cancer leading to more deaths in women in India compared to any other cancer [1]. However breast cancer has been rising steadily in the last 10 years, and for the first time in and thereafter 2012, breast cancer became most common cancer in women in India. [2]

Mastectomy was the preferred treatment modality historically for all stages of breast cancer. Large randomized trials provided the evidence that the breast conserving therapy (BCT) is the treatment of choice, demonstrating equivalent survival compared to mastectomy [3-8]. BCT, characteristically consisting of surgical removal of lumpectomy with wide local excision with negative margins followed by whole breast irradiation (WBI), with the aim of irradiating remaining tumor cells in the tumor bed. The improvement in the overall survival was found with lumpectomy with radiation therapy when the studies were carried out to compare it with lumpectomy alone [7, 9-12]. Use of radiotherapy also demonstrated the reduction in recurrences many fold in the above studies. Reduced long term complications, lesser physhological trauma and better cosmetic outcomes were observed in the patients treated with BCT [7-8].

Standard WBI irradiates the whole breast, which receives up to 45–50 Gy, delivered over 30–35 days, and in most patients, doses to the tumor bed are boosted either by external irradiation or interstitial brachytherapy. These booster doses usually range between 10 and 15 Gy and when the boost is delivered through external beam

radiotherapy, WBI lasts 6–7 weeks. The prolonged treatment is inconvenient for those patients residing away from the radiotherapy centers and contributes to the mastectomy as a treatment choice thus affects quality of life [13-15]. Partial breast irradiation in which limited volume of breast is irradiated around the lumpectomy was explored to reduce overall treatment duration.

1.2 Rationale for Accelerated Partial Breast Irradiation (APBI):

Evaluation of the follow up data from many studies revealed that the majority of the recurrences with both breast-conserving surgery only and breast-conserving surgery followed by whole-breast radiotherapy treatment were within the tumor bed, suggesting that probably partial breast irradiation may be enough for women with smaller risk of recurrence in breast [16-20]. Recurrences in the ipsilateral breast were observed in only 3 to 4% of patients in the areas other than tumor bed [20]. Pathological studies also supported this facts on those women considered appropriate for BCT had the microscopic spread of malignant cells is likely to be within the 1 cm [21-23].

Irradiation of partial breast with a smaller target volume leads to the expectation of lesser radiation doses of nearby organs such as the lungs and heart. Literature also revealed about lung toxicity induced due to radiation of breast cancers after radiotherapy treatment, such as pneumonitis and lung fibrosis [24-25]. Many large trials also reported an increase in mortality for incidence of lung cancer after radiotherapy for breast cancer [26-29]. The reduction in the radiation target volume in breast cancer provides two advantages. The dose per fraction can be increased and accelerated treatment schedule can be achieved with minimum toxicity to the organs at risk as they do not lie within the target volume as compared to whole breast

irradiation where a part of lung and heart in left sided breast cancer may receive larger doses of radiation. Genesis of the Accelerated Partial Breast Irradiation was conceptualize with the fact that with more than 50% reduction in the target volume receiving radical doses of radiation, radiobiologically equivalent doses can be safely delivered over one week duration.

1.3 Accelerated Partial Breast Irradiation (APBI) Techniques:

Rather treating whole breast irradiation, APBI treats only the tumor bed with a 1-2 cm margin. Decrease in the target volume and increase in the dose per fraction resulted in a shorter treatment duration by using APBI technique. Improvement in the patient comfort and reduction in the radiation induced toxicity to the lung, heart, and contralateral breast is due to the shorter overall course of treatment from 6–7 weeks for whole breast radiotherapy to one week for APBI. There are many techniques currently available to implement APBI in radiotherapy clinics, these are: EBRT (external beam radiation therapy), multi-catheter interstitial brachytherapy, balloon brachytherapy, and intra-operative radiation therapy (IORT). All these techniques are entirely different from one another in terms of radiation delivery methods, invasiveness, efficiency, acceptability between radiation oncologist and overall length of treatment. These techniques are extensively reviewed by Njeh et al [30]. The brief description of these techniques is discussed.

1.3.1 APBI using Brachytherapy:

Brachytherapy places radioactive sources either within tumor or in close contact with the tumor volume. The word brachytherapy means short therapy, derives its name from the Greek word “Brachus” means “near”, implying that the irradiation is restricted to volumes in close proximity. The brachytherapy treatment is from the

inside out as the radiation is emitted outwards from radiation source with a sharp fall off dose to nearby tissues. Unlike, in external-beam radiotherapy, radiation traverse normal healthy tissues and organ at risks to reach the target volume contains tumor cells. Therefore, brachytherapy allows the dose escalation with high conformality (i.e.; radiation dose confinement to the tumor volume while sparing normal tissues). Brachytherapy is being used in various clinical cancer sites as a radical treatment modality or as boost along with in combination with external-beam radiotherapy.

1.3.1.a Multi-catheter interstitial brachytherapy (MIB):

Multi-catheter interstitial brachytherapy (MIB) is the earliest technique used in initial APBI studies and it has the largest follow-up [30-39]. Flexible after-loading catheters are placed intra-operatively after lumpectomy using needles. To ensure acceptable coverage of tumor bed with adequate margins, brachytherapy flexible nylon catheters are inserted in multiple planes. The inter-plane and inter-catheter distance are kept 1 to 1.5 cm (Figure 1). The procedure typically requires large number of catheters (typically 15 to 30) to assure adequate coverage by prescribed dose. Multiple nylon tubes are placed in the breast by free-hand approach using stainless steel needle and Peris system guidelines. An experienced radiation oncologist can produce the good geometry implant having excellent dosimetric quality. Currently for MIB high dose rate (HDR) brachytherapy is used. The dose of 34 Gy in 10 fractions or 32 Gy in 8 fractions twice daily for HDR is typically prescribed for the treatment which is biological effective dose equivalent to 45 Gy of the LDR treatments [40].

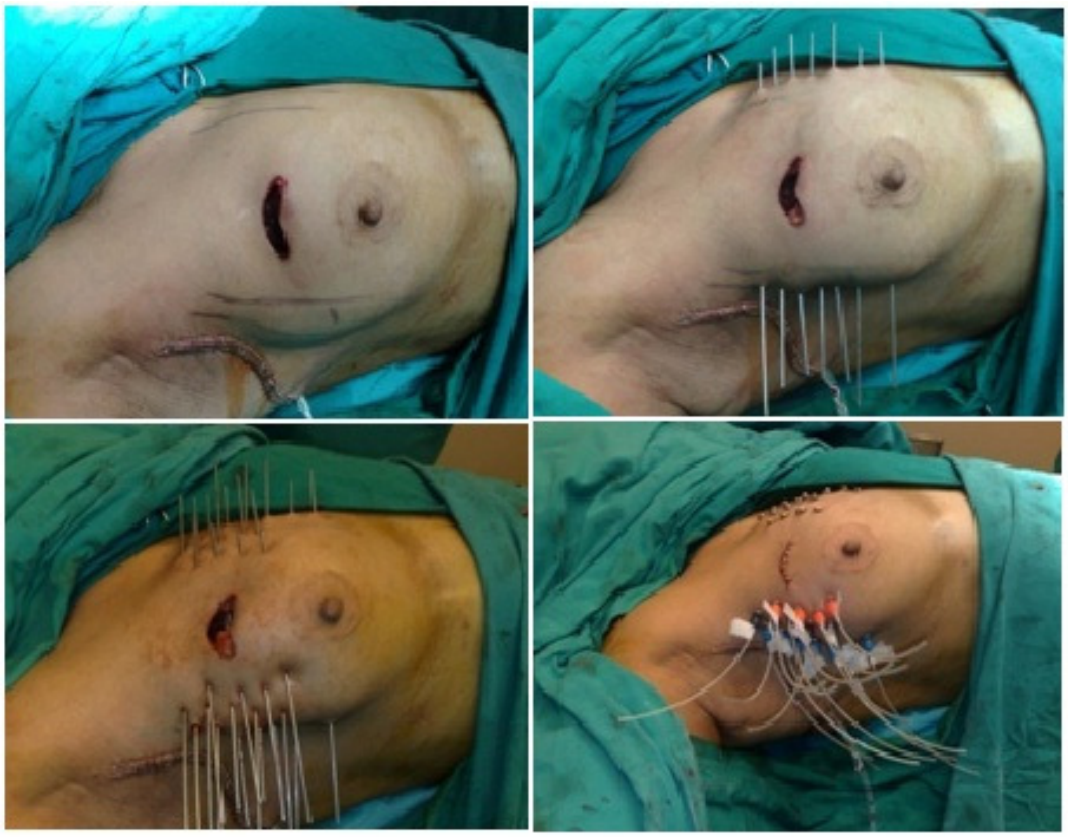
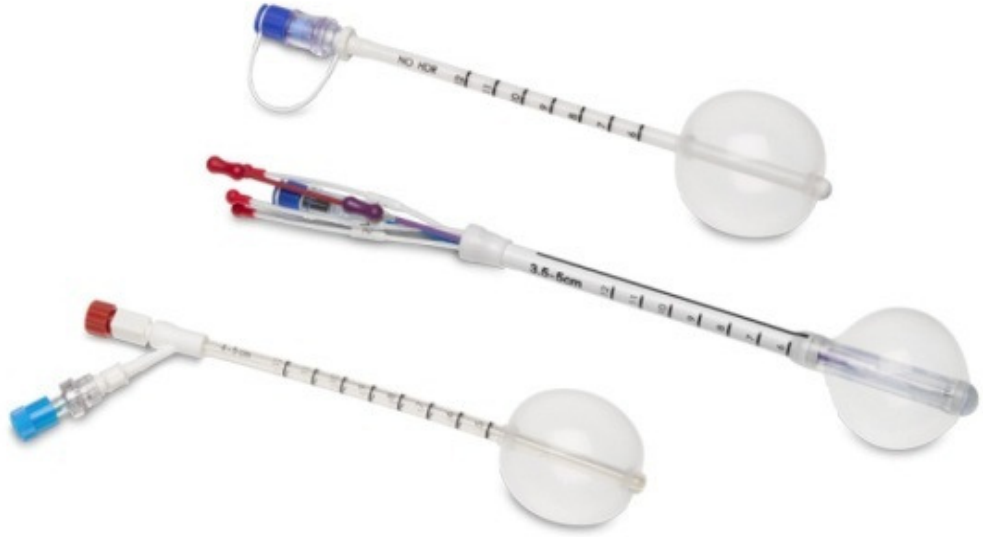


Figure 1: Multi-catheter intra-operative interstitial brachytherapy technique practiced at Tata Memorial Centre a) lumpectomy and marking of implant planes b) and c) insertion of stainless steel needles in different plane d) replacement of stainless steel needle with flexible catheters

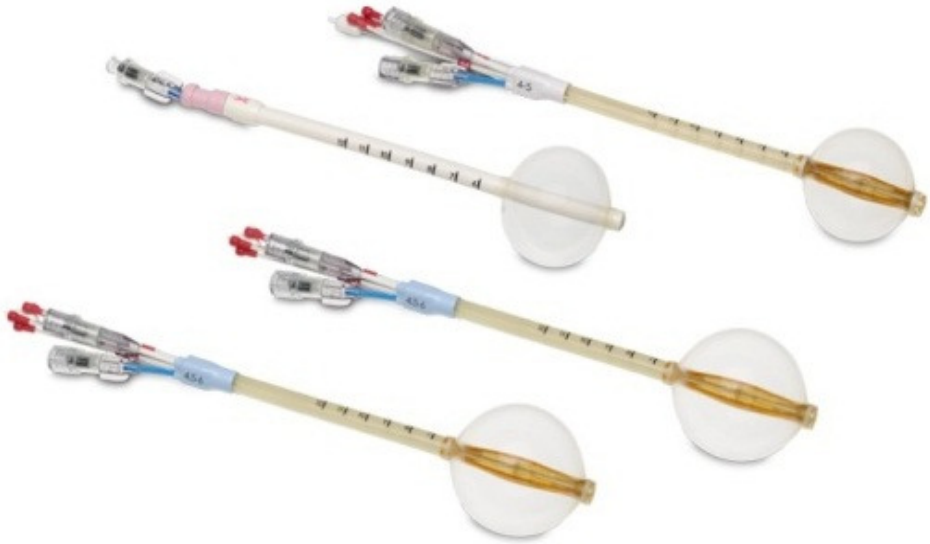
1.3.1. b Balloon-Based Brachytherapy Devices (Memosite and Contura):

The MammoSite brachytherapy system (Hologic, Marlborough, MA) applicator consists of catheter with double lumen having 15 cm length connected to a silicon balloon (Figure 2 a). The dual channel catheter allows entering an Ir-192 HDR brachytherapy source to the central channel which is at the balloon length. Small amount of contrast material is mixed with saline solution for visualization of inflated balloon. The amount of contrast would require to inflate the balloon adequately and to fill the lumpectomy cavity and thus to achieve conformance balloon with lumpectomy cavity. Prescribed dose of radiation is delivered by an Ir-192 radioactive source, which is controlled by remote after-loader with high dose rate brachytherapy machine and the source is inserted into the balloon via the Mamosite catheter. [30, 41-42].

MammoSite technique may not be suitable in patients with small breast because of the requirement for skin-to-cavity distances and which is its major limitation. This limitation was overcome by introducing a MammoSite Multi-lumen device and Contura device (Figure 2 b). In addition to central channel, Contura balloon is having four more channels to accommodate the HDR source around it [30, 43]. Compared with single channel applicator, additional channels of Contura and MammoSite Multi-lumen device provide multiple source positions and thus allow increased flexibility in dose optimization. Therefore the normal tissue and OAR doses can be reduced using these devices. Asymmetric activation of the source dwell positions also allowed greater flexibility in the treatment delivery.



a) MammoSite Balloon applicator and MammoSite Multilumen System (www.hologic.com)



b) Contura balloon applicator (www.hologic.com)

Figure 2: MammoSite applicators a) MammoSite balloon applicator and MammoSite Multilument system b) Contura balloon applicator

1.3.1.c Axxent Electronic Brachytherapy:

Another form of balloon brachytherapy introduced by X-soft (Fremont, CA) is Axxent electronic brachytherapy system [30, 41, 44]. It consists of balloon catheter which is similar to the MammoSite system. The Axxent system is having has a central catheter which allows the source to be inserted in the device (Figures 3 a). There are separate ports to Inflate the balloon and saline and for removal of seroma fluid or air in the lumpectomy cavity. Radiolucent material covers the balloon wall, which can have radio-opaque visualization on a radiograph or axial CT scan. The advantage of the system is no additional radiographic contrast required for visualization. Instead of an Ir-192 high-dose-rate (HDR) source, the Axxent electronic brachytherapy system utilizes a 50 kilo-voltage x-ray source and that makes this system a novel treatment device. X-ray source in the miniature x-ray tube, is inserted into balloon applicator which is kept inside the patient near the tumor bed (Figure 3 b).

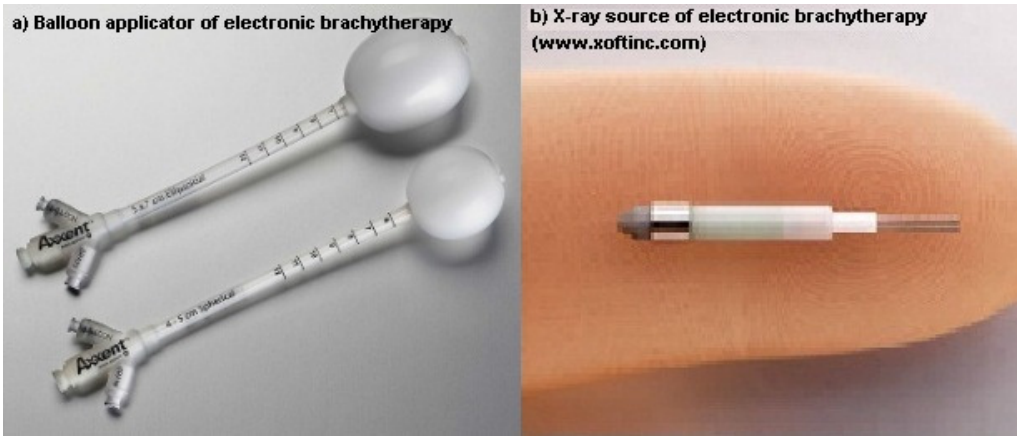


Figure 3 a) Balloon applicators and b) X ray source of electronic brachytherapy

1.3.1.d Hybrid Brachytherapy Devices (SAVI and ClearPath):

Hybrid brachytherpay devices such as Struts Adjusted Volume Implant (SAVI) and the ClearPath was developed as a modification in the single lumen balloon applicator to get the advantages of dosimetic conformality of multicatheter interstitial brachytherapy and ease of insertion in the treatment site.

The SAVI device (Figure 4) have a central strut surrounded by peripheral struts and manufactured by Cianna Medical, Aliso, Viejo, Ca [30, 41, 45]. The peripheral struts are 6, 8 or 10 in numbers and can be differentially loaded with a HDR source. Numbers of struts are depends on the size of the SAVI device. Collapsed form of the device is inserted in through a small incision and then expanded to fit the lumpectomy cavity by expanding the peripheral struts. Three of the peripheral struts have the radio-opaque markers which can be identified at the time of the reconstruction process during the treatment planning.

ClearPath device (North American Scientific, Chatsworth, CA) is similar to SAVI and having inner and outer catheters (Figure 5) [30, 41, 46].. To conform the wall of the cavity, the outer expandable catheters can be expanded like a balloon devise. Six additional plastic tubes are around the central catheter through which the HDR Ir-192 source delivers the radiation. The advantage of ClearPath device over the SAVI is that it is designed in such a way that the radioactive source is never in direct contact with the surrounding tissues.

Figure 4: SAVI brachytherapy device

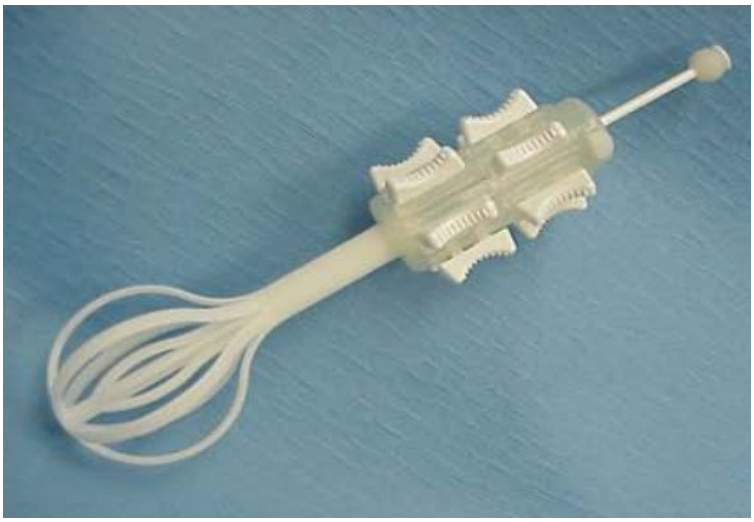


Figure 5: ClearPath brachytherapy device

1.3.2 APBI using External beam radiotherapy:

External beam radiation therapy techniques used for APBI are 3D-conformal radiation therapy (3DCRT) using static photon beams, hybrid photon and electrons beams, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) and proton beam therapy [30, 47-49]. 3DCRT and IMRT are non-invasive techniques and utilized the commonly available equipments in modern radiotherapy departments. The clinical target volume includes the surgical cavity with an adequate margin which is edited from the skin and chest wall to spare them from radiation. A margin for respiratory motion and setup variation is added additionally for EBRT. APBI using 3DCRT offers superior dose homogeneity at the cost of increased dose to normal tissues and organ at risks when compared with brachytherapy.

1.3.3 Intra-Operative Radiation Therapy Techniques:

Intra-operative radiation therapy (IORT) technique delivers radiation doses to the tumor bed directly during surgery using a single fraction. Initially intra-operative radiation therapy devices were not technically advanced; therefore for IORT transportation of the patient from the operating theatre to the treatment room was required. Otherwise IORT system needed installation in custom-built intra-operative radiation therapy theatres [30, 50]. Mobile intra-operative radiation therapy devices were introduced and developed after technological advancement in miniaturization technology. In 1998 Intrabeam device which was the first intra-operative radiation therapy with kilovoltage photons was used [30, 51]. Two other mobile linear accelerators Mobetron and Novac-7, which were capable to generate megavoltage electrons, have become commercially available thereafter.

In our institution we are practicing the mulicatheter interstitial brachytherapy (MIB) technique for APBI. Present thesis is focused around the MIB technique and the uncertainties associated with this technique

1.4 Transition from conventional radiograph based to three dimensional (3D) Computed Tomography (CT) based MIB dosimetry:

Conventionally the dosimetry and treatment planning of interstitial implants had been carried out using a set of orthogonal radiographs. Dosimetric outcome of conventional brachytherapy planning is being evaluated by visualizing the isodoses qualitatively in the orthogonal planes of implant geometry. Dosimetric system used for conventional planning lacks in providing three-dimensional relationship between the volume of isodoses and the anatomical extension of the target volume. Thus tumor coverage may not necessarily correlate with the implant dosimetric quality estimated using the Anderson dose volume histogram. In last decade, anatomy based treatment planning using computed tomography (CT) scans was adopted in the clinics which provides a clinically realistic evaluation of the implant dosimetry on target volume [53-57, 59]. Initially 3D CT based systems were not available for brachytherapy treatment planning. During that era Vicini et al [53] carried out quantitative evaluation on 3D CT images of radiograph based plans by retrospectively translating the dwell positions and dwell times planned for conventional radiograph based 2D plans on to 3D CT data of the patient. They demonstrated the necessity of CT based planning for the clinically realistic dosimetric evaluation of target coverage and dose homogeneity. First report on 3D computed tomography-based planning for multi-catheter partial breast dosimetry was published by Das et al. [54]. Kestin et al [57] used large number of catheters along with the interactive graphical optimization for postoperative image

guided implant technique and demonstrated the improvement in coverage of target volume compared to the 2D planning using radiograph. Cuttino et al. [55] also found improvement in the target coverage with CT guided implants when compare with the postoperative implants guided using fluoroscopic placement. Dosimetric evaluation of 3D CT based optimized plans showed improved target coverage and inhomogeneity when compared with dose point optimization plans generated on radiographs by Major et al [58]. They have compared plans generated using different optimization strategies [58] in patients undergoing postoperative template implants for partial breast irradiation. In our institute we had carried out comparison of the dosimetric outcome of radiograph and computed tomography-based planning using objective parameters such as different dose volume indices and various optimization strategies on the same set of patients undergoing intraoperative interstitial brachytherapy implants for partial breast irradiation [59]. Three-dimensional computed tomography-based dosimetry was found superior compared to conventional two-dimensional radiograph-based APBI planning. Dose volume indices derived from computed tomography-based planning were found useful for evaluating the implant as well as comparing the different brachytherapy plans. Significant improvements in dosimetric conformity over conventional X-ray based plan was observed in graphical optimization plans due to the interactive optimization on the target volume.

1.5 Review of uncertainties in brachytherapy:

In last decade the CT image based three dimensional (3D) brachytherapy for multi-catheter interstitial breast implants was evolved over conventional radiograph based techniques and have been established in clinics [53-59]. The advantages of 3D brachytherapy over conventional brachytherapy planning are to provide clinically

realistic dosimetric information on target and OAR volumes and anatomy based quantitative evaluation using dose volume analysis. It also allows individualized treatment tailoring of dose around the 3D target volume. Uncertainties in 3D image based external beam radiotherapy have been investigated in details during last decades [60-72]. Uncertainties in brachytherapy were considered negligible as the catheters; tumor and surrounding tissues were considered invariable [73]. However, uncertainties in brachytherapy can lead to potential source of errors as the dose gradients are significant beyond the target volume.

Clinical brachytherapy uncertainties were extensively reviewed by Kiristis and colleagues [74]. They have discussed the recommendations of American Association of Physicist in Medicine (AAPM) and Groupe Européen de Curiethérapie – European Society for Radiotherapy and Oncology (GEC-ESTRO) joint report on brachytherapy dosimetric uncertainties (AAPM TG-138) [75]. They have adopted the methodology based on the report of Comité International des Poids et Mésures (CIPM) for evaluating and expressing measurement uncertainty [76], which was further developed by the International Standards Organization (ISO) in the Guide to the Expression of Uncertainty in Measurement (GUM) [77] and by the U.S. National Institute of Standards and Technology (NIST) Technical Note 1297 [78]. The Uncertainty has category in either Type A (statistical) or Type B (everything else) components. The precision of a measurement is the reproducibility among measured value (Type A), however the difference between true value and observed value is the accuracy.

Combining all uncertainty components in quadrature as relative standard uncertainty yielded the overall uncertainty ‘V’. Wich is expressed as Eq. (1) where s_i is the

standard deviation of the mean of multiple measurements and is the quadrature sum of all Type A uncertainties, and u_j is the quadrature sum of all Type B uncertainties.

$$V = 2\sqrt{(s_i^2 + u_j^2)} \quad (1)$$

A coverage factor of 2 (k = 2) to be multiplied with the square root of the quadrature sum of both type A and type B uncertainty to estimate the overall uncertainty (expanded k = 2) for a 95% confidence interval. The uncertainty estimation assumes the observations having normal distribution and the individual components of uncertainty should be expressed with k = 1 as recommended in TG-138 report.

Kiristis et al [74] describes the sources of uncertainty in brachytherapy which includes the uncertainties in source strength measurements, dose calculations in treatment planning system (TPS), heterogeneity effects, dose delivery, imaging and the uncertainty at the patient level. The typical uncertainty in source strength measurements for HDR source was estimated as 1.5 % (k=1) however for treatment planning with HDR source it was 2.6% (k=1) [75]. As the current TPS is having dose calculation algorithms based on AAPM TG-43, uncertainties due to heterogeneities are also involved which is to be estimated for each treatment site [79-81]. The uncertainty in dose delivery such as positional accuracy was estimated as ±1 mm [82], however, maximum contribution of transit dose to measured dose was reported 0.5% due to temporal accuracy [82]. Uncertainties in the imaging may lead to reconstruction errors and subsequent dose to structures which is dependent on clinical disease site.

Uncertainties at the patient level includes structure delineation, applicator reconstruction, inter and intra fraction anatomical variations which needs to be

estimated for each clinical site and technique separately. Review of literature revealed extensive work reporting the uncertainties in mainly for gynecological and prostate brachytherapy [83-94]. Although there are studies addressing the uncertainties in balloon brachytherapy for accelerated partial breast irradiation [95-100], there have been so far very limited data published for uncertainty related to 3D image based breast brachytherapy using multi catheter interstitial implants [101].

1.6 Aims/Objective of the work undertaken for the thesis:

In the present thesis the work was carried out to investigate the uncertainties for CT image based 3D brachytherapy of multi-catheter interstitial breast implants for APBI, which are as follow:

a) Reconstruction errors of catheters for interstitial breast implant using indigenously designed breast phantom.

b) Inter-observer variation in the delineation of the target volume

c) Dosimetric impact of inter-observer variation in target delineation

d) Change in the target volume during course of brachytherapy treatment

The scientific literature relevant to this thesis is summarized in this chapter. However more specific publications are reviewed in the individual chapters. Chapter 3, 4 and 5 of this thesis is already been published in the form of research papers in the peer reviewed international journals; these are denoted by papers 1, 3 and 2 in the publication list.

Chapter 2

Geometrical uncertainties: Reconstruction errors

2.1 Introduction:

Last decade witnessed transition from conventional radiograph based brachytherapy to computed tomography (CT) based three dimensional (3D) conformal brachytherapy [102-105]. Brachytherapy offers steep dose gradient near the sources and active source positions in 3D conformal brachytherapy are loaded in the vicinity of the 3D defined target volume. Therefore, accuracy in the localization of sources inside the catheters plays an important role for overall accuracy in the treatment planning of 3D brachytherapy.

Source localization accuracy during the brachytherapy treatment planning relies on the accuracy in the reconstruction of the catheters. In CT based 3D brachytherapy accuracy of catheter reconstruction depends on the thickness of acquired axial CT slice and the orientation of the catheters with respect to the imaging plane. Conventionally reconstruction accuracy in brachytherapy is being investigated as a part of QA of treatment planning system [106-108]. Many authors explored the reconstruction errors using customized phantom for prostate seed brachytherapy [92, 109-111]. Algorithms for auto-reconstruction were also introduced for faster and accurate reconstruction of brachytherapy catheters [112-113]. Investigation of reconstruction errors and its dosimetric impact were also reported for gynecological brachytherapy [114-115]. In a multi-centre study accuracy of implant reconstruction and dose delivery was determined; however majority used radiograph based localization methods [82]. Limited work was published demonstrating the reconstruction accuracy for breast implant [116]. There is no study reporting systematic investigation of the optimum slice thickness and orientation of the implant. The present work was carried out to investigate the impact of slice thickness and

implant orientation with respect to the imaging plane on the reconstruction errors using an indigenously fabricated breast phantom.

2.2 Materials and methods:

2.2.1 Design and fabrication of indigenous phantom and rotational platform:

A multi-slice 3D breast phantom was indigenously designed and fabricated using Polymethyl-methacrylate (PMMA) sheets. Phantom was constructed by manually cutting of PMMA sheets for external body contours of a representative patient of breast cancer which was having average dimensions among the cohort of 20 patients. Manual milling of the phantom surface was performed to create smooth external body contours. A three plane implant having square geometry with flexible nylon tubes was constructed in the breast phantom. Nylon tubes were placed in the customized grooves made in PMMA sheets. Each plane had four catheters; therefore, in total 12 catheters implant was simulated. To create a standard geometry implant, all tubes kept in straight line with Inter-catheter and inter-plane separation of 12 mm which represented template based implant. Figure 6 shows the phantom with implanted tubes in a square standard geometry. To investigate the reconstruction errors due to rotation of implant with imaging plane a rotating platform with angular scale was fabricated. Figure 7 represent the rotating platform which was fabricated for the study.

2.2.2 Acquisition of CT scan:

GE Light Speed Xtra, (GE Medical Systems, Wisconsin, USA) CT machine was used to acquire the CT images for the study. Lasers on CT system was checked for its accuracy and aligned with the image centre. The rotating axis of the platform

was than aligned with the CT lasers. Radio-opaque markers were kept on the rotating platform which was also used to identify the rotational axis and rotational angle during the reconstruction and planning process. Phantom was placed on the rotating platform and radio-opaque markers were kept in phantom at some known geometric locations on the external surface of phantom to verify the accuracy of the process.

CT scans were acquired with slice thickness of 0.6 mm, 2.5 mm and 5 mm with constant pitch value. A reference scan was acquired in which the implant geometry was kept perpendicular to the imaging plane (90^0) with the minimum slice thickness of 0.6 mm. The phantom was then rotated to various angles (0^0, 5^0, 10^0 and 20^0) and scans with slice thickness of 0.6 mm, 2.5 mm and 5 mm were acquired. All the scans were transferred to Oncentra brachytherapy planning system (Nucletron, an Elekta company, Stockholm, Sweden).

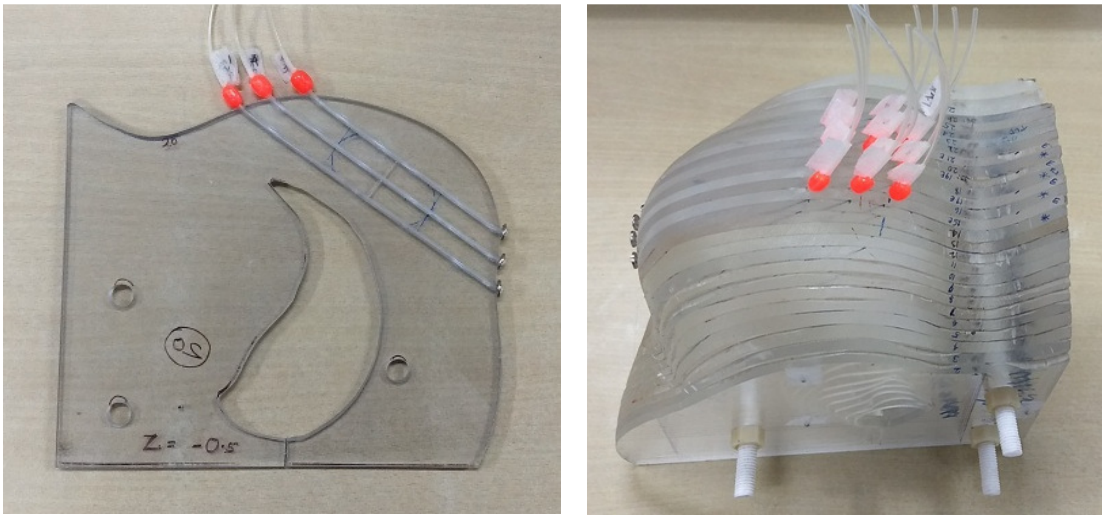


Figure 6: Indigenously designed multi-catheter breast phantom consists of square geometry interstitial implant

2.2.3 Reconstruction of the catheters:

Reconstruction of the catheters was carried out for the CT data of the phantom for all orientation and slice thickness using multi-planar reconstruction with 5 mm step size. Active source dwell positions were loaded in all the tubes till the phantom surface with inter source distance of 20 mm. Active source dwell positions was kept consistent for all CT data sets. Source co-ordinates were noted for each source positions. Figure 8 shows the measurement for angular rotation angle (for verification) of the platform using the markers kept at platform.

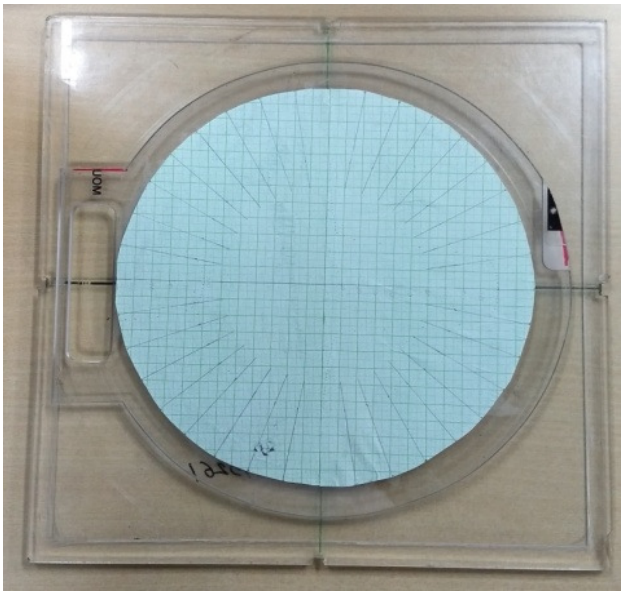


Figure 7: Rotational platform with angular scale

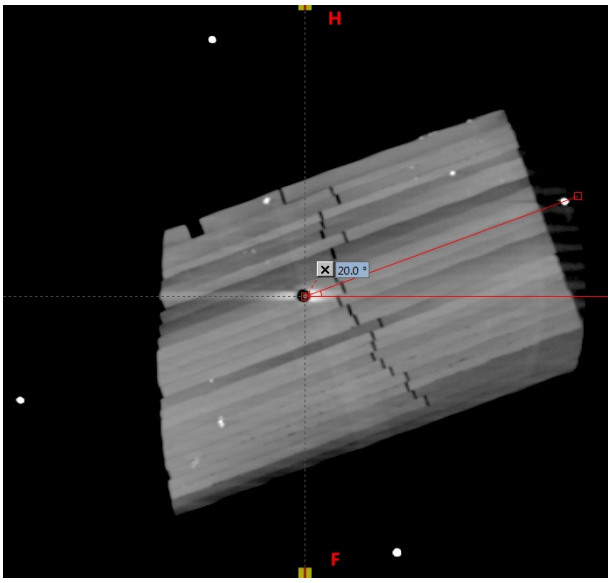


Figure 8: Verification of phantom rotation angle using radio-opaque markers

2.2.4 Coordinate transformation:

The source coordinates of the CT images for 0.6 mm slice thickness acquired with perpendicular implant orientation (90^0) to the imaging plane was taken as reference. Co-ordinate transformation was performed on the source co-ordinates of the other phantom orientation and slice thickness to the reference orientation and compared with the reference source co-ordinates. The Figure 9 shows the co-ordinate transformation method and equation 2 and 3 represents the co-ordinate transformation matrix used in the present work.

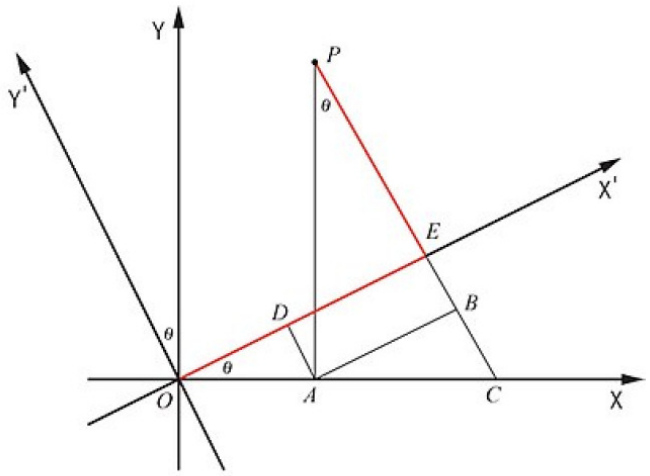


Figure 9: Coordinate transformation method used in present work

$$x' = x\ \cos\theta - y\ \sin\theta \tag{2}$$

$$y' = x\ \sin\theta + y\ \cos\theta \tag{3}$$

2.2.5 Analysis:

Accuracy in the localization of the rotating platform axis was estimated by computing the standard deviation in the coordinates of the rotation axis in axial, longitudinal and vertical direction for all slice thickness and implant rotation. The mean geometrical distance and standard deviation (SD) between corresponding source positions from all CT data sets with reference data set was estimated for investigating reconstruction errors. The SD of mean displacement of dwell positions in axial, longitudinal and vertical direction between corresponding source dwell positions was also evaluated.

2.2.6 Statistics:

Statistical analysis was carried out using commercial Statistical Package for Social Science (SPSS version 20.0, IBM, Chicago). The distribution of mean geometrical distances of the corresponding source dwell positions from the reference data set was tested using Shapiro-Wilk test and found to be normally distributed. Standard deviation (SD) of the histogram was taken as the uncertainty of the geometric position. One-way ANOVA test with Bonferroni post hoc analysis was used to estimate the statistical significance of the mean geometrical distances with slice thickness and the implant orientation.

2.3 Results:

Figure 10 shows the multi-planar images of the phantom in a) sagittal, b) axial and c) coronal planes with reference data set which was acquired for 90^0 catheters orientation and 0.6 mm slice thickness. The reference data set represents the maximum spatial information of implanted catheters. Figure 11 shows the multi-planar images of the phantom in a) axial, b) sagittal and c) coronal planes which was acquired for 5^0 orientations and 5mm slice thickness. In all 3 planes reference images of figure 1, the implanted catheters were clearly visible with adequate spatial information of implanted catheters for reconstruction. However, for the corresponding images in figure 2, loss of spatial information was observed due to the larger slice thickness and its orientation which was near parallel to the imaging plane. Maximum reconstruction error (SD = 0.3 mm) in the localization of rotating platform axis was observed in longitudinal direction, which was the direction of slice thickness. Similar observation was found for the corresponding source dwell positions where the maximum reconstruction error (SD = 1.4 mm) was observed for the localization of

dwell positions in the longitudinal direction for 5 mm slice thickness and 5^0 implant orientation when individual components of source coordinates were analyzed.

Figure 12 represents the mean relative distance between the corresponding source dwell position for the different slice thickness and various orientations of the implanted tubes from scanning plane and Figure 13 represents the respective standard deviations. Table 1summarizes the mean geometrical distance and Standard deviations (SD) between corresponding dwell positions for all implant orientations and slice thickness. There was significant increase in mean (SD) geometrical distance by increasing the slice thickness for all implant orientation. Significant increase in mean (SD) geometrical distance was also observed when implant orientation angle increased from parallel (0^0) orientation. The maximum mean geometrical distance (SD) of 1.7 (0.9) mm was observed for 5.0 mm slice thickness and parallel implant orientation. The mean geometrical distance and SD tends to decrease with increasing the angle between the imaging plane and catheter plane, however it increases with slice thickness. For 20^0 angular orientation of implanted tubes from imaging plane and 0.6 mm slice thickness, the minimum reconstruction error (SD) of 0.3 mm was observed. Smallest slice thickness found to have consistent and least reconstruction errors for all implant orientations.

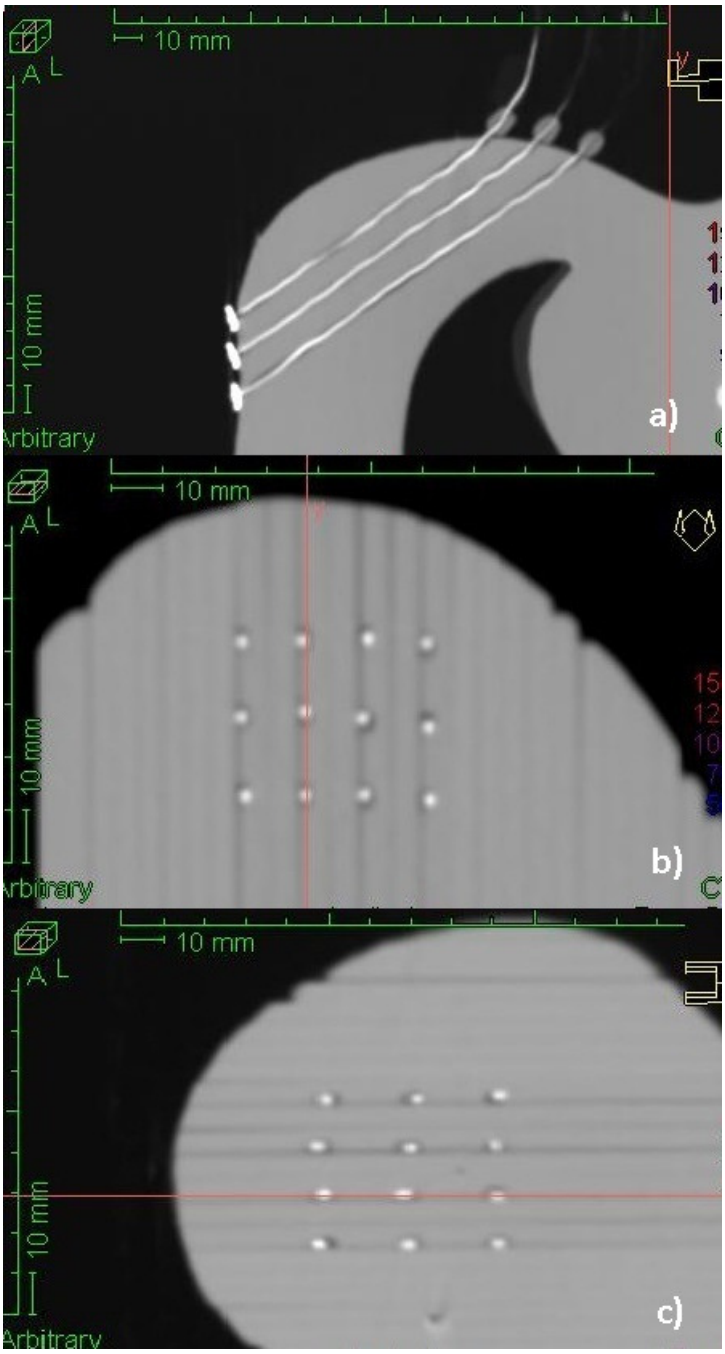


Figure 10: Multi-planar images of the phantom in a) sagittal, b) axial and c) coronal planes with reference data set which was acquired for 90^0 catheters orientation and 0.6 mm slice thickness.

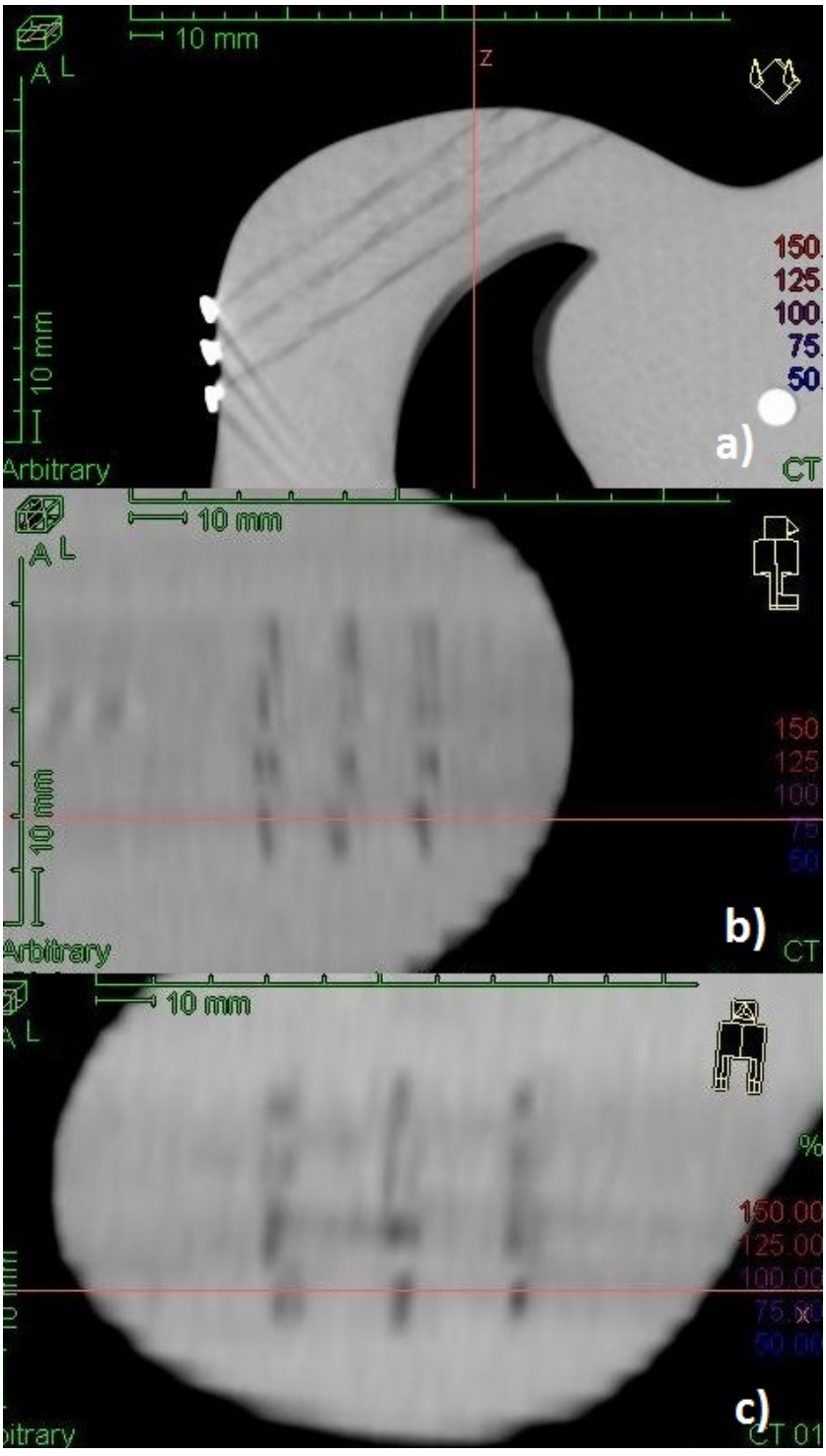


Figure 11: Multi-planar images of the phantom in a) axial, b) sagittal and c) coronal planes which was acquired for 5^0 orientation and 5mm slice thickness.

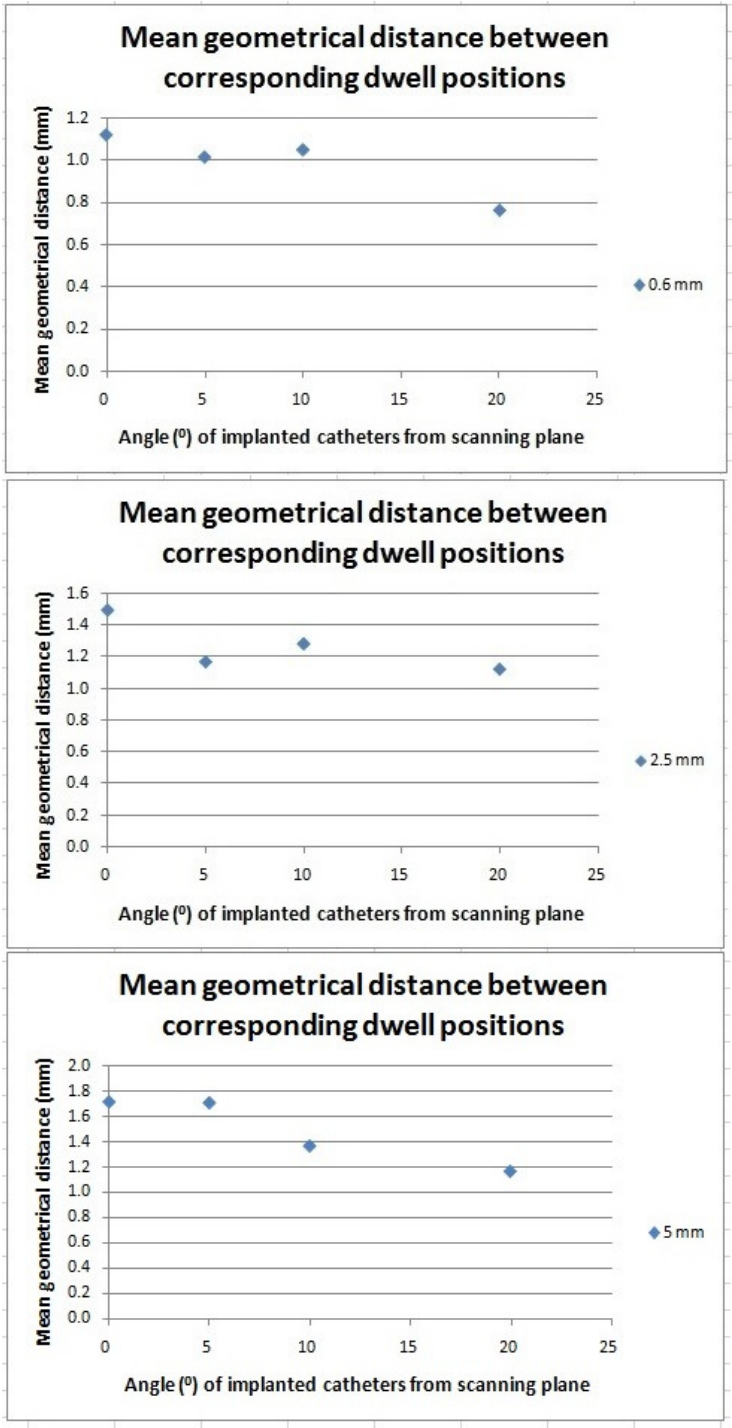


Figure 12: Mean relative distance between corresponding dwell positions for a) slice thickness 0.6mm, b) slice thickness 2.5 mm and c) slice thickness 5 mm

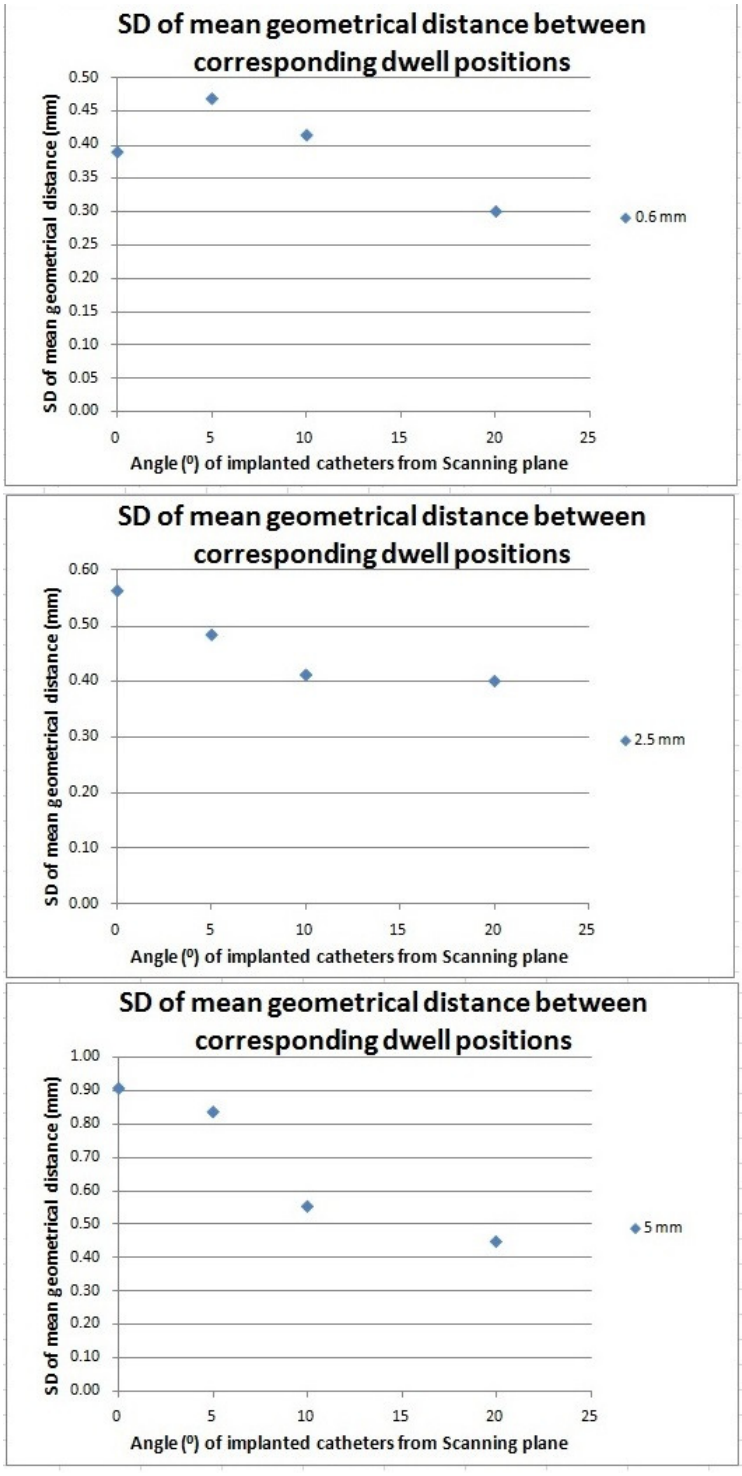


Figure 13: SD of mean relative distance between corresponding dwell positions for a) slice thickness 0.6mm, b) slice thickness 2.5 mm and c) slice thickness 5 mm

Table 1: Mean geometrical distance and Standard deviations (SD) between corresponding source dwell positions for all implant orientations and slice thickness

	Implant orientation (^{0}) from imaging plane	Slice thickness (mm)			ρ value*	Significant pairs
		0.6	2.5	5.0		
Mean± Standard deviation of geometrical distancebetween corresponding source dwell positions	0^0	1.1±0.39	1.5±0.56	1.7±0.90	0.000	a, b
	5^0	1.0±0.47	1.2±0.48	1.7±0.83	0.000	b, c
	10^0	1.1±0.41	1.3±0.41	1.4±0.55	0.005	b
	20^0	0.8±0.30	1.1±0.40	1.2±0.45	0.000	a, c
ρ value*		0.000	0.001	0.000		
Significant pairs		f, h, i	d, f	f, h		

**One-way ANOVA test, statistical significance (0.05) is reported between couples from post hoc Bonferrani analysis;*

[a]: 0.6 mm slice thickness vs 2.5 mm slice thickness,

[b]: 0.6mm slice thickness vs 5.0 mm slice thickness,

[c]: 2.5mm slice thickness vs 5.0 mm slice thickness.

[d]: 0^0 implant orientation vs 5^0 implant orientation,

[e]: 0^0 implant orientation vs 10^0 implant orientation,

[f]: 0^0 implant orientation vs 20^0 implant orientation,

[g]: 5^0 implant orientation vs 10^0 implant orientation,

[h]: 5^0 implant orientation vs 20^0 implant orientation,

[i]: 10^0 implant orientation vs 20^0 implant orientation,

2.4 Discussions:

The reconstruction of the catheters is one of the important steps in the brachytherapy planning process and the accuracy of localization of sources depends on the accuracy of catheter reconstruction. Active source positions in the vicinity of the target volume, steep dose gradients and rapid fall off the doses demands the overall accuracy in 3D conformal brachytherapy more stringent.

Reconstruction accuracy in brachytherapy is essentially a part of quality assurance (QA) of a treatment planning system [106]. Moreover, reconstruction accuracy plays an important role while implementing any new treatment technique using any new applicator, catheters, implant tubes and needles. Reconstruction accuracy of different techniques and treatment sites are studied by many authors using customized phantoms. As commissioning of new applicator/catheters system requires carrying out quality checks of each and every catheter for integrity and determinations of offset valuesfor CT/MRI based planning. Radiograph, autoradiograph alongwith CT/MRI images of the applicator/needles are recommended to be acquired for verification [114 - 115]. However most of these procedures are carried out using image acquisition in which axis of applicator and catheters are kept perpendicular to CT scanning plane in order to get maximum information of the applicators on the acquired images.

Siebert et al. developed a phantom for the verification of commercial 3D seed reconstruction algorithm for prostate brachytherapy and the accuracy of localization of seeds was investigated for radiograph based localization [109]. The phantom was later used for multi-centric study to test seed reconstruction accuracy for CT and X-ray based reconstruction [110]. CT and MRI compatible phantom was also developed to

investigate the intrinsic accuracy of seed detection for both imaging modalities for prostate brachytherapy. In another study by Schmid et al, the needle reconstruction accuracy for ultrasound-guided prostate brachytherapy was investigated in a specialized prostate phantom [111].

For CT based 3D interstitial brachytherapy planning, source localization and catheter reconstruction is performed on the acquired CT scans. In many practical scenarios of interstitial breast implant, the implanted catheters are rarely perpendicular to imaging plane. Sometime catheters are near parallel to the axial plane. The acquisition of inadequate spatial information of catheters due to larger slice thickness and orientation has an impact on reconstruction uncertainties. Literature revealed limited work demonstrating the reconstruction accuracy for breast implant [116]. In the present work, specific phantom simulating the breast implant with a standard geometry was indigenously fabricated and systematic evaluation of reconstruction uncertainty for various implant orientation and image acquisition was carried out.

In the present work, the maximum variation in mean geometrical distance was 1.7 (SD = 0.9) mm which was observed for the largest slice width of 5 mm. Hensley et al [116] reported the uncertainties in the range of 1.1 mm to 2.8 mm. They have compared radiograph reconstruction with CT reconstruction for phantom and series of 33 patients. They observed larger uncertainty for patients than phantom due to patient movements. The limitation of the present work is that we did not simulate breathing motion in phantom to estimate the uncertainty due to breathing motion. The present study is carried out for standard implant geometry. Practically for an actual free hand breast implant, majority of time the implanted tubes are in different planes and also never follows straight line geometry. Therefore, reconstruction errors for an actual

breast implant might be larger than we observe in the present work. The reconstruction errors also depend on the slice thickness and the inter-catheter separation. Theoretically if slice thickness is comparable with the inter-catheter separation and catheters are aligned with the imaging plane, the parallel orientation may acquire the maximum information of the tube with least reconstruction errors. This is also reflected in our results, as the smallest slice thickness having the lesser errors with parallel orientation. Many of the reported studies addressed dosimetric impact of the reconstruction errors [108, 114, 117]. Another limitation of the present work is that we did not evaluate the dosimetric impact of the reconstruction errors for the breast implants.

In last decade the auto reconstruction capabilities were also developed in CT based brachytherapy planning system [112, 113]. It was demonstrated that auto reconstruction algorithm efficiently reconstructs the catheters with 90% success rate with mean geometrical errors varying from (0.38±0.22) mm to (1.41±0.44) mm with a mean value of (0.87±0.36) mm [112]. However, we have observed that in our institution for intra-operative breast implants, presence of seroma and air in the lumpectomy cavity influence the efficiency of auto reconstruction and require larger manual corrections in auto reconstructed catheters. Also the radio-opaque buttons at the tip and connector end also hinders the efficiency of the auto reconstruction algorithm.

In a systematic study for prostate seed reconstruction, Siebert et al [110] observed that when the slice thickness of CT scan reaches to 4 or 5 mm the accuracy of the CT seed reconstruction decreases in longitudinal direction. In our work we observed similar findings for the largest slice thickness (5 mm) with had highest

reconstruction errors. We also observed the largest errors in the direction of the slice thickness (longitudinally) among all three directions. Present study also demonstrates that reconstruction errors are significantly less for the smallest slice thickness. However, reduction of the slice thickness may leads to higher exposure to the patient from the imaging dose. Moreover, there are the risks of secondary cancer for long term surviving patients from imaging dose [118]. Also selection of minimum slice thickness for each and every patient may leads to the large number of images which may cause problems of data management in a longer term. Therefore, selection of optimum slice thickness for every individual patient is required. Present work also suggests that is an implant is near parallel to the imaging plane, patient may be oriented to $\geq 10^0$ to get optimum reconstruction accuracy.

2.5 Conclusion:

Reconstruction errors were found to be larger when catheter orientations are near to parallel with imaging plane. Significant reduction in the reconstruction errors was observed when slice thickness decreases and angle of implanted catheters from imaging plane increases. Smallest slice thickness showed the least reconstruction errors.

Chapter 3

Inter-observer variation in target volume delineation

3.1 Introduction:

Accuracy in the delineation of the volumes is an important step in the planning process of radiotherapy. Errors in the delineation may result in the geographic miss and excessive irradiation of surrounding normal tissues which may reflect in clinical outcomes. Inter-observer variation in the delineation of the volumes may have effect on the dose volume histogram resulting in differences in the plan acceptability between radiation oncologists. Inter-observer variability in delineation of volumes are systematically reviewed and documented for other sites such as gynecological and prostate brachytherapy in radiation oncology [73-74, 84, 86, 88, 94], however limited studies are published for multi-catheter interstitial breast brachytherapy [101].

In this chapter ~~i~~nter-observer variation in target volume delineation has been investigated.

3.2 Purpose:

Accelerated partial breast irradiation (APBI) for early stage breast cancers using MIB has shown promising early results for selected subgroup of patients. [30-39] The APBI technique offers overall reduction of treatment time to 1 week compared to 3-6 weeks of standard whole breast radiation therapy due to the irradiation of confined target volume around the lumpectomy cavity (LC).

Conventionally dosimetry of MIB for APBI was carried out using localization X-ray radiographs which limited the three dimensional (3D) definition of the target volume, thereby resulting in larger irradiated volume. [58, 59] During the last decade, 3D image based brachytherapy has evolved which provided clinically realistic dosimetric information on patient anatomy [55-56, 58-59,119].

Active source positions in 3D brachytherapy are loaded in the vicinity of the 3D defined target volumes. Hence accurate delineation of the LC and clinical target volume (CTV) is essential to provide adequate dosimetric coverage and conformity. Variations in delineation of LC and CTV could result in the differences in treatment volumes and may have impact on dosimetric as well as clinical outcome. Inter-observer variability of tumour bed and target delineation for APBI using external beam radiotherapy has been extensively studied [68-72], however available literature is sparse for MIB of breast implants [101].

APBI using MIB was started at our centre in the year 2000 and initial 115 patients were treated by radiograph based planning [120]. We adopted 3D brachytherapy since 2005 and have reported excellent local control rate in 140 women with long term follow-up [36].The present work investigated the inter-observer variation amongst radiation oncologists in delineation of LC and CTV for APBI treatment using MIB in a busy tertiary cancer centre.

3.3 Materials and methods:

3.3.1 Patient Selection and Implant Technique:

Twenty patients with treated with APBI using MIB were retrospectively included for the study. Intra-operative placement of nylon tubes in the lumpectomy cavity using open cavity technique was performed for patients with a tumor size up to 3 cm, negative margins and axillary lymph nodes. The technique allowed a direct visualization of tumor bed. The tumor bed was marked with five radio-opaque clips placed at the superior, inferior, medial and lateral borders and in the centre of the posterior wall of the cavity.

3.3.2 Imaging:

All patients underwent CT scans with 0.3 cm slice thickness on Somatom Emotion scanner (Siemens Medical Systems, Germany) and images were exported to the Oncentra 4.3 brachytherapy treatment planning system (TPS) (Elekta AB, Stockholm, Sweden). Median time for surgery to CT imaging was 3 days.

3.3.3 Cavity Visualization:

We developed a cavity visualization index (CVI) to standardize the delineation process for open cavity technique practiced at our institution. The visualization of cavity was ranked using three parameters: clarity of cavity (includes visualization of seroma, air in cavity and surgical clips), distinction of cavity with adjacent breast tissues and distinction of cavity with muscle tissues. The four point numeric index ranging from CVI = 0 i.e. poor, all parameter unsatisfactory (poor visualization of cavity which merges with adjacent tissues) to CVI =3 i.e. excellent, all parameters satisfactory (representing excellent visualization of cavity with clear distinction from breast and muscle tissues) was used in the current study (Figure 14).

Five radiation oncologists who specialize in the treatment of breast cancer participated as observers for this study. All observers independently assigned a CVI for each patient. The mode of the CVI was taken as CVI index for each patient.

3.3.4 Delineation and treatment planning:

Each observer contoured the LC on the axial CT scans. Consistent window level and width were used for delineation. Observers were blinded from reviewing other contours. CTV was obtained by uniform volume expansion with 1 cm around

the LC. CTV was edited by limiting the skin by 0.5 cm and up to the chest wall. For brachytherapy CTV was considered as planning target volume (PTV).

3.3.5. Analysis:

The analysis was done by computing spatial concordance (conformity index, CI) of LC and CTV, which is ratio of common volume and encompassing volume drawn by all observers (CI_{common}). The generalized conformity index (CI_{gen}) was computed for LC and CTV.

The generalized conformity index (CI_{gen}) defined as the ratio of the sum of all overlapping volumes between pairs of observers and the sum of all overlapping and all non-overlapping volumes between the same pairs [121].

$$CI_{gen} = \frac{\sum_{pairsij} |Ai \cap Aj|}{\sum_{pairsij} |Ai \cup Aj|}$$

Centre of mass (COM) was computed and mean distance for each pair wise comparison between COM of LC and CTV was quantified for all patients [68]. Ratio of maximum and minimum volumes among observers for each patient was computed. Relative SD (SD/mean) of LC and CTV volumes were also computed.

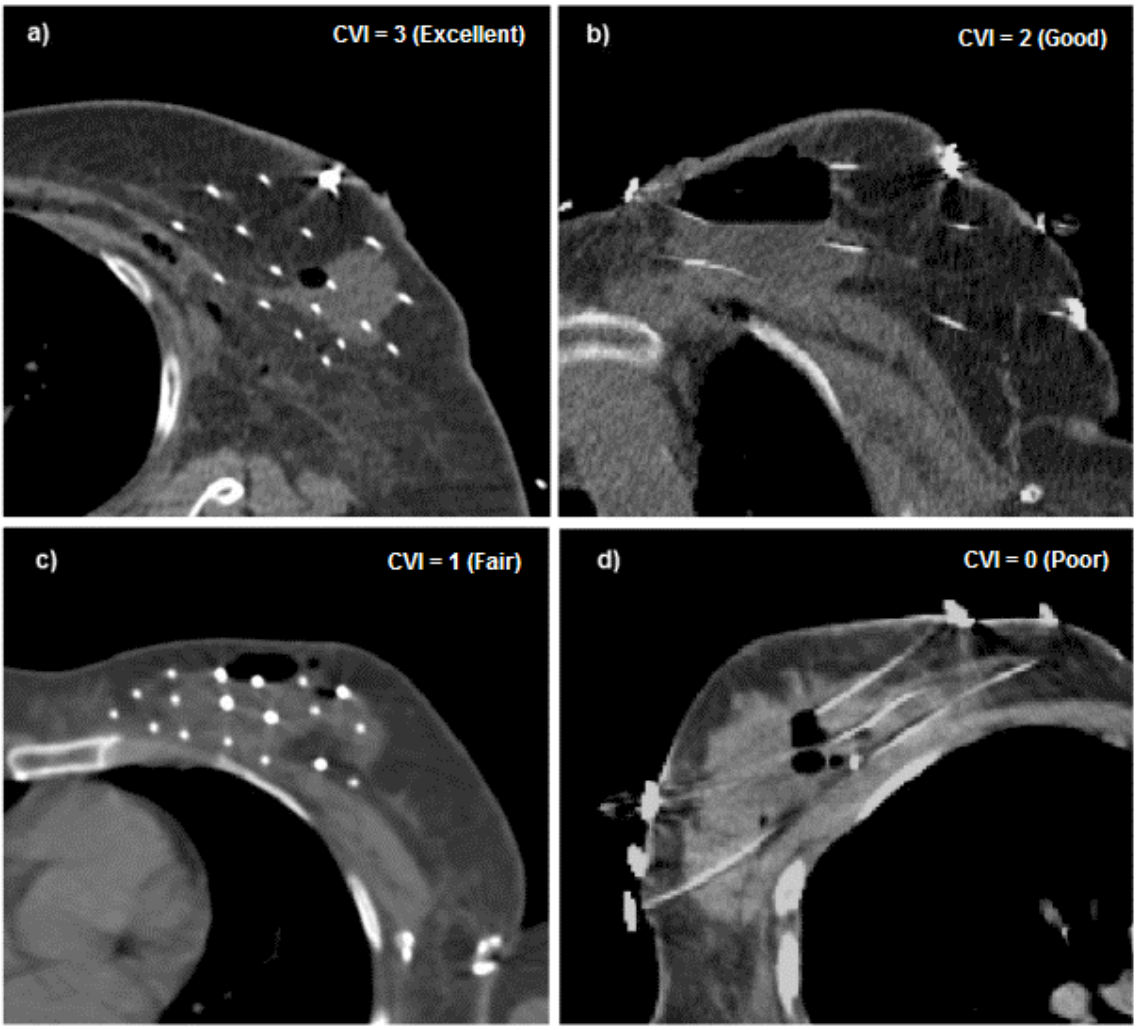


Figure 14: The cavity visualization index, a) Cavity is well visualized with distinction from breast/muscle tissues, b) Cavity is visualized but not clearly distinguishable with either breast or muscle tissue, c) Cavity is visualized but not clearly distinguishable with both breast and muscle tissue, d) All parameters are not satisfactory

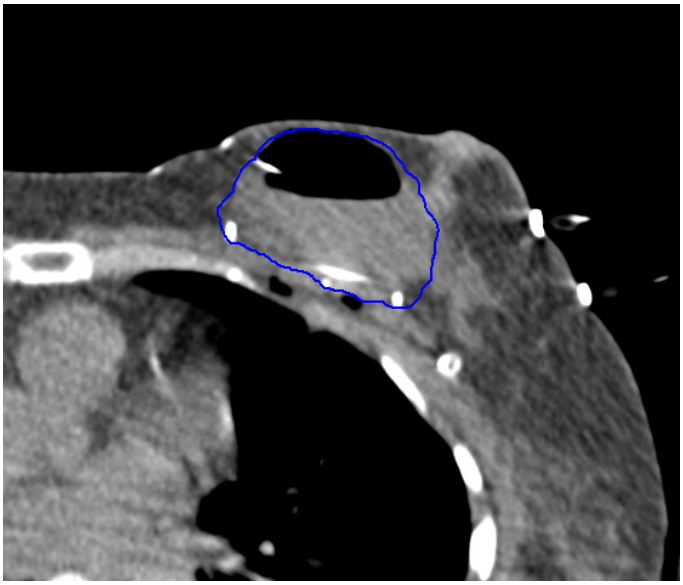


Figure 14 e): Axial CT scan representing the delineation of LC using the radio-opaque markers, seroma and air in the lumpectpomy cavity

3.3.6 Statistics:

Statistical Package for Social Sciences (SPSS version 20.0, IBM, Chicago) was used for analysis. The coefficient of variation (COV) of volumes was computed. Wilcoxon signed-rank test was used to compare the volume of LC and CTV between each physician pair. One way ANOVA test was used to compare the measure of variability for LC and CTV with CVI levels.

Table 2: Comparison of CTV volumes among all observers

Pair wise Comparison *	Median difference in CTV volume (cm^3)	ρ value ^
Δ_{21} (CTV2 – CTV1)	9.1	0.019
Δ_{31} (CTV3 – CTV1)	30.0	0.000
Δ_{41} (CTV4 – CTV1)	22.0	0.001
Δ_{15} (CTV1 – CTV5)	6.9	0.970
Δ_{32} (CTV3 – CTV2)	15.0	0.001
Δ_{42} (CTV4 – CTV2)	12.9	0.021
Δ_{25} (CTV2 – CTV5)	5.9	0.015
Δ_{34} (CTV3 – CTV4)	2.1	0.218
Δ_{35} (CTV3 – CTV5)	25.7	0.000
Δ_{45} (CTV4 – CTV5)	16.9	0.001

** For pair wise comparison data was arrange to keep median difference positive*

^ Wilcoxon signed-rank test

Abbreviations:

CTV – Clinical Target Volume

Δ– Difference in the volume

$V_{100\%}$ – Volume of prescription isodose

Table 3: Lumpectomy cavity (LC) and Clinical target volume (CTV) variability

	Lumpectomy cavity (LC)			Clinical target volume (CTV)		
	Mean	Median	SD	Mean	Median	SD
Volume (cm^3)	75.8	68.0	30.9	159.8	146.6	58.8
CI_{common}	0.54	0.56	0.09	0.58	0.58	0.08
CI_{gen}	0.74	0.75	0.06	0.76	0.78	0.05
COM shift (cm)	0.27	0.26	0.10	0.34	0.33	0.13
V_{max}/V_{min}	1.32	1.26	0.19	1.36	1.34	0.22

Abbreviations:

LC – Lumpectomy cavity, CTV – Clinical target volume, SD – standard deviation, CI_{common} – Conformity index among all observers, CI_{gen} – Generalized conformity index for all observers, COM shift – shift in the centre of mass of the volume, V_{max} – maximum volume among observers, V_{min} – minimum volume among observers

3.4 Results:

3.4.1 Cavity visualization:

Out of 20 patients, 4 (20%) patients had CVI = 1, 10 (50%) patients had CVI = 2 and 6 (30%) patients had CVI = 3.There were no patients with CVI = 0.

3.4.2 Contoured volumes:

Table 2 represents the pair wise comparison of CTV using Wilcoxon signed-rank test along with the median difference in volumes for all observers. Significant

difference was observed in the median volume of CTV between 8 pairs (out of total 10 pairs) of observers.

Summary of variability measures (CI, COM shift and V_{max}/V_{min}) for volumes (LC, CTV) are given in Table 3. Median volume, COM shift, CI_{common} and CI_{gen} for LC were 68 cm^3, 0.26cm, 0.56 and 0.75, however the values for CTV were 146.6 cm^3, 0.33cm, 0.58 and 0.78 respectively. The mean COV (±SD of mean) for LC was 0.11 (±0.06) however it was0.12 (±0.05) for CTV.

3.4.3 Cavity visualization index and volumes:

Table 4 summarizes the variability of LC and CTV and its relation to CVI. Significant decrease in COM shift of LC and CTV was observed with increase in CVI.Cases having fairy visible LC (CVI = 1) showed large median COM shift of 0.46cm for CTV and 0.41 cm for LC. Cases with excellent visualization of cavity (CVI = 3) had COM shift below 0.32 cm and 0.26 cm for CTV and LC respectively. Significant increase of CI_{common} and CI_{gen} for LC and CTV was found with increase in CVI. For CVI = 3, CI_{common} and CI_{gen} for CTV was 0.65 and 0.81, however for CVI = 1 the respective values were 0.50 and 0.72. The mean (SD) of $V_{max}/V_{min}$was 1.32 (0.19) for LC and 1.36 (0.22) for CTV. Significant decrease in median of V_{max}/V_{min} of LC ($\rho < 0.029$) and CTV ($\rho < 0.008$) volumes was found with increase in CVI. The Bonferroni post hoc analysis revealed the significant variation ($\rho < 0.05$) in all variability parameters for group of CVI=1 and CVI=3, however all variability parameters for group of CVI=2 and CVI=3 was found insignificant. For group of CVI=1 and CVI=2, variation in C_{common}, C_{gen} of LC and V_{max}/V_{min} of CTV was found significant ($\rho < 0.05$). The mean relative SD of LC and CTV volumes were 10.9% and 11.7% respectively.

Table 4: Cavity visualization index (CVI) and variability of LC and CTV volumes with median value and range

CVI	1	2	3	ρ value*
n	4	10	6	
COM shift of LC (cm)	0.41 (0.29 – 0.46)	0.26 (0.19 – 0.52)	0.18 (0.12 – 0.26)	0.004
COM shift of CTV (cm)	0.46 (0.37 -0.62)	0.35 (0.2 – 0.61)	0.26 (0.17 – 0.32)	0.019
CI_{common} LC	0.48 (0.33 - 0.49)	0.56 (0.40 - 0.66)	0.61 (0.53 - 0.65)	0.01
CI_{common} CTV	0.50 (0.39 -0.56)	0.59 (0.45 - 0.70)	0.65 (0.51 - 0.68)	0.02
CI_{gen} LC	0.69 (0.59 - 0.69)	0.75 (0.64 - 0.81)	0.78 (0.74 - 0.82)	0.004
CI_{gen} CTV	0.72 (0.65 - 0.75)	0.78 (0.69 - 0.83)	0.81 (0.73 - 0.83)	0.018
V_{max}/V_{min} (LC)	1.42 (1.36 - 1.75)	1.26 (1.10 - 1.73)	1.19 (1.07 - 1.29)	0.029
V_{max}/V_{min} (CTV)	1.57 (1.44 - 2.02)	1.29 (1.14 - 1.68)	1.20 (1.15 - 1.50)	0.008

** One-Way ANOVA test*

Abbreviations:

LC – Lumpectomy cavity,

CTV – Clinical target volume,

CI_{common} – Conformity index among all observers

CI_{gen}– Generalized conformity index for all observers

V_{max} – maximum volume among observers

V_{min} – minimum volume among observers

3.5 Discussions:

Target delineation in 3D MIB for APBI is critical as it involves irradiation of partial breast volume alone which is at higher risk of tumor relapse if not treated adequately. Moreover, uncertainty in the whole treatment procedure is contributed by target volume delineation which is substantiated by geometric uncertainties in external beam radiotherapy but not so in brachytherapy. This uncertainty is taken care by PTV margins in external radiotherapy but in bracyhtherapy the concept of PTV is not used. Errors are less forgiving and more severe in brachytherapy as sources lie within the target region which if not defined precisely can lead to reversal of the therapeutic ratio. Variation in CTV volumes had an impact on implant dosimetry which resulted in different treatment volumes among the five observers in the current study. Literature search revealed many studies on inter-observer variations [68-72] however limited work has been published for MIB for APBI using open cavity surgery [101].

Quantification of visualization of cavity was developed and used in many published studies [69, 122].The scale/score of cavity visualization in other published studies had 5 or 6 steps of scoring, mostly applicable for post operative cavities. The median time for CT imaging after lumpectomy and intra-operative catheter placement for our patients was 3 days; therefore cavity was always present in all of our cases. We have developed our own cavity visualization index (CVI) for the intra-operative brachytherapy technique practiced at our Institute. CVI which is used in the present work had 4 steps of scoring. The excellent visualization of cavity for our system has CVI = 3 in contrast to the other system [69, 122] where Score '5' represent the best visualization.

Present study demonstrated the correlation of CVI with variability of delineation, better visualization resulted in better concordance and decreased COM shift. For CTV median spatial concordance (CI_{gen}) was improved from 0.72 to 0.81 and median COM displacement of CTV was decreased from 0.46cm to 0.26 cm as the CVI increases from '1' to '3'.Similar findings were reported by Landis et al [68] for PTV, their values of CI_{pair} had improved from 0.57 to 0.87 and median COM were decreased from 0.69 cm to 0.15cm with increase in visualization score.

The only published study of inter-observer variation of APBI using mutli-catheter brachytherapy was by Major et al [101]. The observed spatial concordance (CI_{common} and CI_{gen}) of cavity in post implant CT using guidelines was 0.36 and 0.56, and the respective values of CTV were 0.54 and 0.70. Our data showed better concordance on post implant planning CT images with values of CI_{common}, CI_{gen} for cavity and CTV was 0.54, 0.74 and 0.58, 0.76 respectively. This could be due to the differences in the timing and technique of implant as well as imaging protocol of the two institutes. In the Budapest series, catheters were not implanted immediately after lumpectomy, pre-implant CT imaging was done in all cases and catheters were inserted with the help of a template. However, at our institute, the intra-operative placement of the catheters was done immediately after lumpectomy as a single procedure without any pre-planning imaging. Free hand technique was utilized due to direct visualization of the tumor bed.

Struikmans et al [72] had observed mean CI of 0.56 for boost CTV for external beam radiotherapy and they had concluded that each institute should determine their inter-observer variability with respect to target volume. Reported CI of seroma volume for three observers by Petersen et al [69] was 0.61. Similar to our observation

they had reported significant correlation between seroma clarity and conformity of seroma volumes.

Mean Vmax/Vmin of LC and CTV in our study was 1.32 and 1.36 respectively. Major et al [101] have demonstrated that with contouring guidelines the mean Vmax/Vmin ratio of CTV was decreased from 2.2 to 1.2 for oncologists having experience in open cavity surgery; however it was 2.8 for observers without open cavity experience in absence of guidelines.

Recently GEC ESTRO breast cancer working group (II) has published recommendations for the target delineation for accelerated or boost partial breast irradiation [123]. Total safety margins 2 cm for CTV in all 6 directions was recommended. The safety margins include surgical resection margins around the tumour. It was also recommended to have safety margin for CTV of at least 0.5 cm whenever surgical margins are larger than 2 cm. However they were unclear whether recommended safety margin for CTV are sufficient to account for inter-observer and intra-observer contouring variation. At our centre we used 1 cm margin from the cavity for CTV in majority of the patients. This essentially is due to wider surgical margins as can be seen from the low margin positive rates reported earlier [36]. GEC ESTRO also recommended the method to determine the boundaries of lumpectomy cavity utilizing seroma and surgical clips. For present study the visualization of seroma, air in cavity and surgical clips were used to define the clarity of cavity for CVI index.

Another way of reducing the uncertainties is to have standardised institutional protocols for image acquisition and target volume delineation. Critical evaluation and review by peers and constant training help to reduce the interobserver variations

further. The limitation of our work is that we have not investigated the role of other imaging modalities (Ultrasonography, Magnetic Resonance Imaging etc) in addition to CT for improvement in delineation of LC as we had carried out the study retrospectively. Major et al [101] have discussed and reviewed the role of other imaging modalities for delineating the tumor cavity wherein the authors conclude that there is a need of further investigation in this area.

3.6 Conclusion:

Significant inter-observer variation in delineation of LC and CTV was observed for intra-operative multi-catheter partial breast brachytherapy. Inter-observer variability was found to be significantly related to CVI. Cases in which the visualization of LC was excellent, demonstrated the smaller variability in the delineation of LC and CTV.

*** *Publication:*** *This chapter is reproduced from the following publication which is a research article arises from the present thesis.*

Upreti RR, Budrukkar A, Wadasadawala T, Misra S, Gurrum L, Pathak R, Dehspande DD. "Interobserver variations of target volume delineation and its impact on irradiated volume in accelerated partial breast irradiation with intraoperative interstitial breast implant." Journal of Contemporary Brachytherapy; 2017:9(2); 139-145.

Chapter 4

Dosimetric impact of inter-observer variation in target volume delineation

4.1 Introduction:

Conformal radiotherapy requires accurate delineation of target volume and inter-observer variation in delineation is a potential source of error in radiotherapy [124]. APBI using MIB is established as an alternative to whole breast irradiation with excellent results for a selected subgroup of patients [30-39]. Three dimensional (3D) computed tomography (CT) based MIB allows conformal planning as it produces steep dose gradient beyond the target. Thus, inter-observer variation in target delineation is likely to have an impact on dosimetric and clinical outcomes. Studies evaluating dosimetric impact of inter-observer variability in target delineation have been conducted for APBI with external beam radiotherapy [70,125]. To the best of our knowledge, no published data exists on the dosimetric impact of inter-observer variation in target delineation for intraoperative breast implants. We have quantified inter-observer variation in delineation of lumpectomy cavity (LC) and clinical target volume (CTV) for intraoperative breast implants in last chapter [126].The present study is carried out to investigate the impact of the inter-observer variation on dose volume indices (DVI's) for graphically optimized plans.

4.2 Materials and methods:

4.2.1 Patient Selection and Imaging:

Twenty patients of early stage breast cancer of APBI were retrospectively included for the study. The tumor bed was identified using 5 radio-opaque clips placed in the lumpectomy cavity intraoperatively as described in last chapter. Catheters were placed intraoperatively in the same sitting as the surgery. Planning CT scan was acquired on

Somatom Emotion (Siemens Medical Systems, Erlangen, Germany) and images were transferred to Oncentra brachytherapy TPS (v 4.3, Elekta).

4.2.2 Delineation and treatment planning:

Five radiation oncologists who specialized in treatment of breast cancer contoured LC and CTV on axial CT scans using most appropriate and consistent window level and width setting and were blinded from reviewing contours of other observers [126]. Prior to delineation of contours, visualization index of LC was determined to standardize the delineation process. Clarity of the LC (which includes visualization of seroma, surgical clips and air in the cavity), distinction of cavity from the adjacent breast and muscle tissues was used to assess the cavity visualization which is discussed in the last chapter. The CTV included lumpectomy cavity with 1cm margin all around to ensure a minimum of 2 cm margin from the edge of the primary tumor [123,126,127,128]. CTV was subsequently cropped by 0.5 cm from skin anteriorly and up to the pectoralis muscle/facia posteriorly.

One hundred geometrically optimized treatment plans were made by a single planner for all CTV contours in each patient. Source step size was kept to 5 mm. Variations in active source positions in each catheter for all CTV's were analyzed to access the impact of target delineation variability on active dwell positions. Plans were than graphically optimized (local optimization) to get maximum coverage of CTV with prescription dose for each observer. The planning and treatment of intra-operative APBI is carried out during the immediate post-op period at our centre. Previous work showed that the average CTV volume of our patients is larger than most published APBI series [59,119]. It was also observed that underdose to the CTV in those patients having air in seroma cavity anteriorly and where it extends close to

skin [59, 119]. Therefore, during treatment planning we aimed at achieving CTV coverage of ≥ 80% and dose homogeneity index (DHI) ≥ 0.75 for our patients. The dose to ipsilateral breast were also limited [volume of ipsilateral breast receiving 150% (V_{150}) and 200% (V_{200}) of prescription dose ≤ 70cm^3 and 20 cm^3 respectively] as per recommendations from National Surgical Adjuvant Breast and Bowel Project (NSABP) B39/ Radiation Therapy Oncology Group (RTOG) protocol 0413 [129].

4.2.3 Analysis:

The inter-observer variation in LC and CTV delineation was investigated and reported in previous chapter [126]. Brachytherapy plans for all the observerswere comparedusing DVI's like coverage index (CI), external volume index (EI), overdose volume index (OI), conformal index (COIN) and plan quality index (PQI) [119,130–132]. Details of DVI's are described in Table 5 (a). Plans made for CTV of all observers were evaluated for CTV of every individual observer. Also plan made for CTV of an individual observer was evaluated for the CTV of rest of the observers. A total of 2500 evaluations were carried out for all 5 DVI's with 500 evaluations for each DVI's. For each patient, plans which were found to have reduction of ≥ 5% and ≥ 10% in CI compared to the planning objectives of CTV of any observer were reported. Relative SD (SD/mean) of CI and COIN was computed to estimate dosimetric uncertainty of inter-observer target delineations.

In addition, other dosimetric parameters were also computed which are described in Table 5 (b). The volume of prescription isodose (V_{100}) and total reference air karma (TRAK) was computed for all plans. The spatial concordance (conformity index, CI_{common}) of V_{100} was then computed for all observers (Table1 b).The indices for spatial concordance by Kouwenhoven et al [121] were proposed for comparing

target volume delineation made by several observers. However, for this study these were used to describe the variation in the size and shape of V_{100} generated for optimized plans among observers. The coverage of each CTV with common volume of prescription dose (V_{100_common}) was also computed among the observers for comparison. Pair-wise computation of CTV coverage was also carried out by calculating the mean coverage of CTVs over all 10 pairs among 5 observers with common prescription volume of respective pairs (V_{100_pair}) with respective CTV's (Table1 b).

For the initial plans which were geometrically optimized, the breast volume received prescription dose ($V_{100\%}$) and total reference air kerma (TRAK), spacial concordance (CI_{common}) of prescription dose $V_{100\%}$ was computed for all observers. Additionally for every patient the maximum/minimum values of prescription dose volume and TRAK was computed.

The impact of change in volume of CTV on various DVI'swas investigated by analyzing a plot between mean relative CTVs (RCV) of an observer and meanDVI'sof all observer plans on the same CTV (Table 1b). Additionally, the mean %variation in CTV (ΔCTV) of each pair among 5 observers was estimated and compared with mean % variation in CI (ΔCI), OI (ΔOI), EI (ΔEI) and COIN (ΔCOIN)of CTV for respective pair. The correlation between them was also estimated.

We also investigated the method to counteract the dosimetric variation due to CTV delineation. The prescription dose was increased ($Plan_{Modified}$) for the plans with poor dosimetric coverage for all CTV's to meet the planning objectives and their impact on DHI and COIN was reported.

4.2.4 Statistics:

Statistical Package for Social Sciences (SPSS version 20.0, IBM, Chicago) was used for analysis. Normality of distributions of DVI'swas tested with Shapiro–Wilk test. Comparison was done using Paired t–test when both samples had normal distribution and Wilcoxon signed-rank test for related samples was used when any sample among the pair deviated from normal distribution and $p < 0.05$ was considered statistically significant. Pearson correlation was carried out between % variations in CTV volume with % variation of various dose volume indices.

4.3 Results:

4.3.1 Impact of inter-observer variation on source loading:

Table 6 summarizes the variation in the source dwell positions from the median source loading among 309 implanted (mean –15.6, SD – 3.3) tubes for all 20 patients due to target delineation variability. Majority of implanted tubes (64.2%) showed variations in the active source positions along the catheters although the delineation variability of CTV was in all dimensions. 18 (5.8%) catheters found to have no active dwell positions in any one observer's brachytherapy plans due to absence of target volume at peripheral locations of CTV in 10 cases. No changes in the source positions was observed in 29.8% catheters however another 29.8% and 17.5% tubes showed variation of 0.5 cm (1 dwell position) and 1 cm (2 dwell position). Variation larger than 5 cm was observed in 9.3% catheters.

4.3.2 Impact on geometrically optimized plans:

Impact of interobserver variation on dosimetric parameters for plans with geometrical optimization is presented in Table 7. Median prescription dose volume

$V_{100\%}$ was 134.2±43,7 cm^3 (range 74.4 – 229.6 cm^3). The mean observed Max/Min value of $V_{100\%}$ was 1.18 (range 1.03 to 1.56) however its variation with CVI was found insignificant. The mean Max/Min value of TRAK was 1.11 (range 1.03 to 1.35).

4.3.3. Impact of inter-observer variation on graphically optimized plans:

Figure 15 a) shows the axial image of representative patient having LC with clearly identified margins and figure 15 e) represents LC having indistinct margins. Figure 15 b), c) & d) demonstrate smaller inter-observer variation in delineation of LC, CTV and its impact on prescription isodose respectively. However figure 15 f), g) & h) shows larger variation in delineation of LC, CTV and prescription isodose respectively.

Table 8 a) summarizes maximum percentage variation in mean DVI'swhen plans made for CTV of all observers were evaluated for CTV of any individual observer. Maximum variation($\rho<0.05$) of 6.3%,8.7%,7.4%,3.5% and 34.9% was observed in CI, COIN, OI, PQI and EI respectively when plans made for CTV of all observers were evaluated for CTV of any individual observer. Table 8 b) represents maximum percentage variation in DVI'swhen plans made for CTV of individual observer was evaluated for CTV of all observers. Maximum variation ($\rho<0.05$) of 10.6%,11.4%,10.6%,4.8% and 72.7% was observed in CI, COIN, OI, PQI and EI respectively when plans made for CTV of individual observer was evaluated for CTV of all observers.

Table 5: Indices used for plan evaluation and comparison

	Indices	Definition	Formula
a) Dose volume indices*	Coverage Index (CI)	Fraction of the CTV receiving a dose equal to or greater than the prescription dose	CTV_{100} / V_{CTV}
	Dose Homogeneity Index (DHI)	Fraction of breast tissues receiving a dose between 100% and 150% of the prescription dose	(V_{100} - V_{150}) / V_{100}
	External Volume Index (EI)	Ratio of volume of the normal breast tissue outside the CTV receiving a dose equal to or greater than the prescription dose to the volume of CTV	(V_{100} - CTV_{100})/V_{CTV}
	Overdose volume Index (OI)	Fraction of CTV receiving a dose equal to or greater than two times of reference dose	CTV_{200} / V_{CTV}
	Conformal Index (COIN) $	Coverage of the CTV by the prescription dose and also the unwanted irradiation of normal tissue outside the CTV with prescription dose	(CTV_{100} / V_{CTV})* (CTV_{100} / V_{100})
	Plan Quality Index (PQI) #	Sum of CI, DHI and COIN	CI+DHI+COIN
b) Other dosimetric parameters	Spatial concordance of V_{100_common} (CI_{common})	Ratio of common volume and encompassing volume of $V_{100}$for plans of all observers	V_{100_common}/ $V_{100\_encompassing}$
	CTV coverage with V_{100_common}	Coverage of CTV with common volume of prescription isodose	V_{100_common} / V_{CTV}
	CTV coverage with V_{100_pair}	Coverage of CTV with paired volume of prescription isodose of respective pairs of observers	V_{100_pair} / V_{CTV}
	Relative CTV volume (RCV)	Mean CTV volume of any observer for all patients normalized with the smallest CTV volume among observers	Mean CTV volume / smallest mean CTV volume

Abbreviations:

V_{CTV} - Volume of CTV

CTV_{100} - Volume of CTV receiving a dose equal to or greater than the prescription dose,

CTV_{200} - Volume of CTV receiving a dose equal to or greater than two times of the prescription dose,

V_{150} - Volume of normal breast receiving 1.5 times of prescription dose,

V_{200} - Volume of normal breast receiving equal to or greater than two times of prescription dose

V_{100_common} - Common volume of prescription dose among plans of all observers

V_{100_pair} – common volume of prescription dose among plans of pairs

CI_{common} – Conformity index (spatial concordance) among all observers

CI_{pair} –. Conformity index (spatial concordance) among pairs of observer

RCV – relative CTV volume

[*] *Dose volume Indices - Meertens, H et al, Brachytherapy from radium to optimization. Nucletron International 1994;300-306.*

[$] *Conformal Index - Baltas D et al, Int J Radiat Oncol Biol Phys1998;40:515–524.*

[#] *Plan Quality Index - Cholewka A et al, J Contemp Brachytherapy2013; 4: 227-231.*

Table 6: Variations in active dwell positions due to target variability

Variations in dwell positions	Variation in cm	No of catheters	% of total catheters
0	0	92	29.8
1	0.5	92	29.8
2	1.0	54	17.5
3	1.5	24	7.8
4	2.0	14	4.5
5	2.5	4	1.3
10	5.0	21	6.8
15	7.5	8	2.5

Table 7: Impact of interobserver variation on dosimetric parameters for geometrically optimized plans

	Min	Max	Median	Mean	SD
$V_{100\%}$ (cm^3)	74.4	229.6	134.2	135.1	43.7
CI_{common} of $V_{100\%}$	0.52	0.90	0.76	0.75	0.11
Max/Min of $V_{100\%}$	1.03	1.56	1.15	1.18	0.13
TRAK (cGy at 1m)	0.18	0.32	0.24	0.24	0.04
Max/Min of TRAK	1.03	1.35	1.09	1.11	0.07

Abbreviations:

$V_{100\%}$–Breast volume in cm^3 receiving prescription dose

Max/Min – Ratio of maximum and minimum values among all observers

TRAK – Total reference air kerma in cGy at 1meter

Table 9 to Table 13 summarize the dosimetric impact of inter-observer variations on mean CI, COIN, OI, EI and PQI respectively in details for all 2500 evaluations. The mean±SD of CI and COIN ranged from 0.756±0.076 to 0.840±0.070 and 0.591±0.090 to 0.673±0.06 respectively. The mean±SD of OI and EI ranged from 0.065±0.010 to 0.074±0.011 and 0.140±0.084 to 0.369±0.210 respectively. The

highest PQI for the plans ranged from 2.22 to 2.26.The mean±SD DHI of plans of all observers was in the range of 0.749±0.013 to 0.753±0.018. A decline of ≥ 5% and ≥ 10% in the CI of any CTV from planning objectives was observed in 42% and 14% plans respectively when plans were evaluated for CTV of all observers. The values of mean relative SD are summarized in Table 14**.** The maximum mean relative SD of CI and COIN was 5.7% and 7.1% respectively.

Impact of CTV variability on dosimetric parameters is summarized in Table 15**.** The observed mean±SD of V_{100}, V_{150} and V_{200} was 160.7±52.1cm^3, 39.5±12cm^{3}and 13.8±3.4cm^3 respectively. CI_{common} of V_{100} and TRAK was 0.70±0.09cGyand 0.27±0.05cGy respectively. The mean coverage of CTV with common volume of prescription dose (V_{100_common}) among observers was 73.1% (range, 54.4%–87.3%). However, the mean coverage of CTV with paired prescription dose volume (V_{100_pair}) among respective pairs of all observers was 77.9% (range, 63.1%–92.2%).

Figures 16 present the plot between mean relative CT volume among observers and mean DVI's. An increase in RCV resulted in reduction of CI, EI and OI. This however led to an improvement in COIN. Figure 17 a) to d) presents the plots between the mean % variations in the CTV volume (Δ CTV) of each pair among 5 observers and mean %variation in CI (ΔCI), OI (ΔOI), EI (ΔEI) and COIN (ΔCOIN) of CTV for respective pair. The ΔCI, ΔOI, ΔEI and ΔPQI linearly negatively correlated with ΔCTV and this was statistically significant ($\rho<0.05$) correlation r = -0.957, -0.970, -0.971 and -0.753 for ΔCI, ΔOI, ΔEI and ΔPQI respectively. However, the mean % variation in COIN (ΔCOIN) positively correlated with ΔCTV and this was also statistically significant ($r=0.967$, $\rho<0.000$).

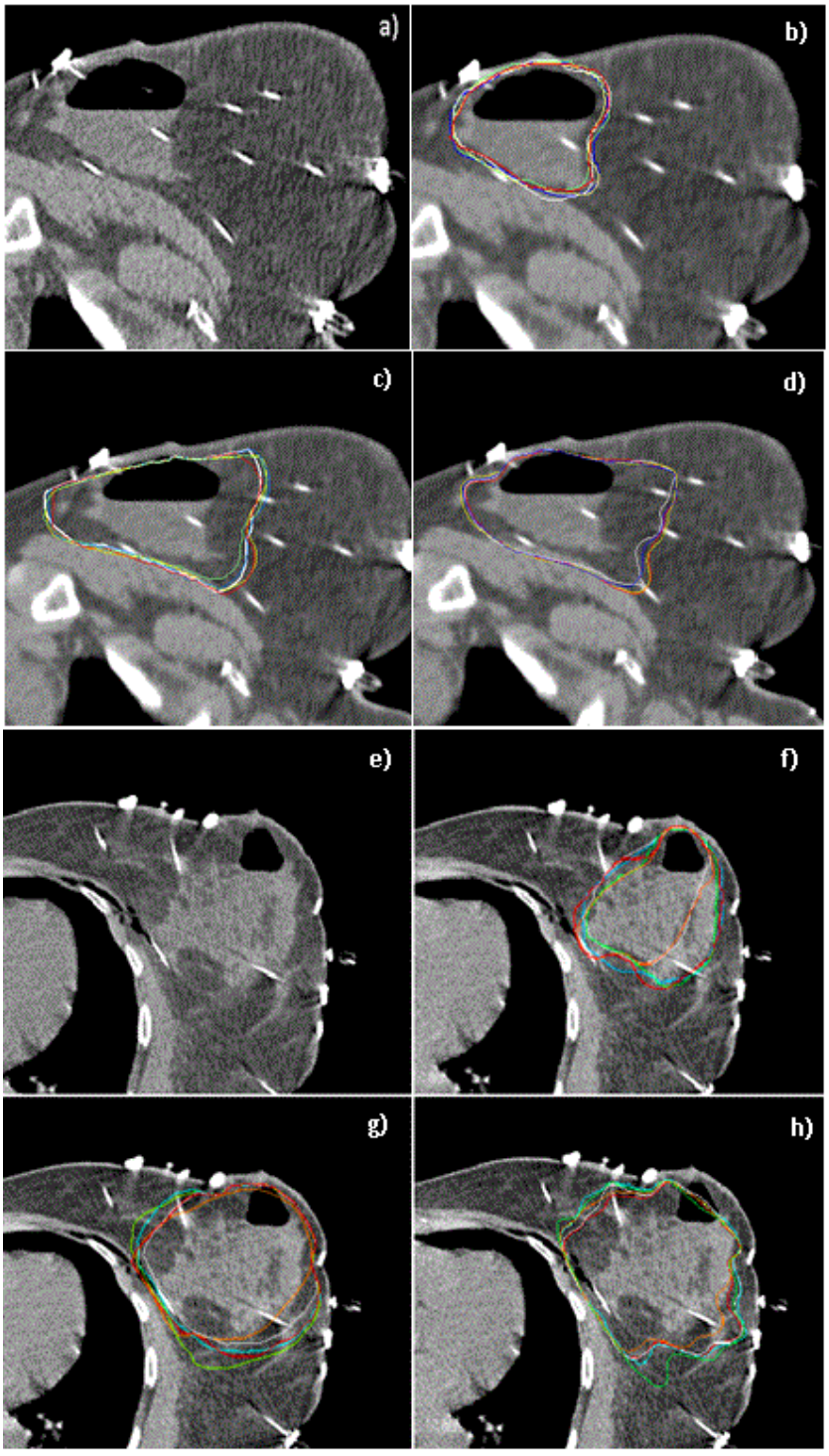


Figure 15: a) Axial image of representative patient having lumpectomy cavity with clearly identified margins, b) Inter-observer variation in delineation of lumpectomy

cavity among all observers, c) Inter-observer variation in delineation of clinical target volume among all observers, d) Impact of Inter-observer variation on prescription isodose, e)Axial image of representative patient having lumpectomy cavity with indistinct margins with adjacent tissues, f) Inter-observer variation in delineation of lumpectomy cavity among all observers, g) Inter-observer variation in delineation of clinical target volume among all observers, h) Impact of Inter-observer variation on prescription isodose. (isodose shown are for graphically optimized plans)

Table 8: Maximum percentage variation in mean dose volume indices yielded from the analysis of 2500 evaluations for all 5 dose volume indices for graphically optimized plans

	Table 4 a) Plans made for CTV of all observers evaluated for CTV of any individual observer				
	Coverage Index (CI)	**Conformal Index (COIN)**	**External volume Index (EI)**	**Overdose volume Index (OI)**	**Plan Quality Index (PQI)**
CTV O1	1.2	8.2#	34.9#	4.2*	3.0*
CTV O2	5.2*	6.4*	25.3#	5.0*	3.3*
CTV O3	6.3*	5.6#	29.2#	4.2*	2.8*
CTV O4	6.1*	4.6*	29.5#	3.3*	3.1*
CTV O5	4.9*	8.7#	26.5#	7.4*	3.5*
	Table 4 b) Plans made for CTV of individual observer was evaluated for CTV of all observers				
	Coverage Index (CI)	**Conformal Index (COIN)**	**External volume Index (EI)**	**Overdose volume Index (OI)**	**Plan Quality Index (PQI)**
Plan O1	10.6*	7.6#	67.0#	10.6*	4.8*
Plan O2	5.7*	9.2*	72.7#	5.1*	3.3*
Plan O3	6.0*	11.4*	71.2#	7.1#	2.8*
Plan O4	6.6*	10.0#	63.4#	6.5*	2.2*
Plan O5	8.0*	8.2*	69.3#	10.1*	3.5*

Statistical significance ($\rho < 0.05$) is reported between couples from paired t – test and wilcoxon signed-rank test[#] (t-test was carried out for sample having normal distribution and wilcoxon signed-rank test for related samples which deviates from normal distribution)*

Abbreviations:

CTV O1, CTV O2, CTV O3, CTV O4 and CTV O5 – Clinical target volume delineated by Observer 1, Observer 2, Observer 3, Observer 4 and Observer 5

Plan O1, Plan O2, Plan O3, Plan O4 and Plan O5 – Optimized plan made on CTV of Observer 1, Observer 2, Observer 3, Observer 4 and Observer 5

Table 9:

Mean (SD) and median of coverage index (CI) resulted from analysis of 500 evaluations of CTV of 5 observers on 20 patients and 5 plans of each observer for graphically optimized plans

	Coverage Index (CI)					
	Plan O1	**Plan O2**	**Plan O3**	**Plan O4**	**Plan O5**	**ρ**
CTV O1	0.839 (0.070) 0.833	0.833 (0.079) 0.832	0.840 (0.070) 0.836	0.835 (0.063) 0.834	0.830 (0.078) 0.823	-
CTV O2	0.787 (0.078) 0.784	0.829 (0.071) 0.808	0.824 (0.073) 0.813	0.814 (0.060) 0.802	0.807 (0.080) 0.794	a, b, c, f, g,i
CTV O3	0.756 (0.076) 0.757	0.790 (0.078) 0.779	0.805 (0.067) 0.792	0.781 (0.064) 0.774	0.783 (0.078) 0.790	a, b, c, d, e, h,i
CTV O4	0.759 (0.071) 0.760	0.786 (0.073) 0.772	0.791 (0.070) 0.786	0.807(0.061) 0.791	0.775 (0.081) 0.768	a, b, c, f, h, I, j
CTV O5	0.799 (0.079) 0.809	0.823 (0.071) 0.791	0.831 (0.068) 0.824	0.821 (0.066) 0.821	0.839 (0.064) 0.832	a, b, c, d, g, h,i
ρ	k, l, m, n, o, p, s, t	l, m, o, p, s, t	l, m, o, p, s, t	k, l, m, o, r, s, t	k, l, m, o, p, q, s, t	

Statistical significance ($\rho < 0.05$) is reported between couples from paired t– test;
a – Plan O1 vs Plan O2, b –Plan O1 vsPlan O3, c–Plan O1 vsPlan O4, d –Plan O1 vsPlan O5, e –Plan O2 vsPlan O3, f –Plan O2 vsPlan O4, g –Plan O2 vsPlan O5, h –Plan O3 vsPlan O4, i–Plan O3 vsPlan O5, j –Plan O4 vs Plan O5
k– CTV O1 vs CTV O2, l – CTV O1 vs CTV O3, m – CTV O1 vs CTV O4, n – CTV O1 vs CTV O5, o – CTV O2 vs CTV O3, p – CTV O2 vs CTV O4, q – CTV O2 vs CTV O5, r – CTV O3 vs CTV O4, s – CTV O3 vs CTV O5, t – CTV O4 vs CTV O5

Table 10:

Mean (SD) and median of conformal index (COIN) resulted from analysis of 500 evaluations of CTV of 5 observers on 20 patients and 5 plans of each observer for graphically optimized plans

	Conformal Index (COIN)					
	Plan O1	**Plan O2**	**Plan O3**	**Plan O4**	**Plan O5**	**ρ**
CTV O1	0.648(0.048)	0.609(0.080)	0.601(0.075)	0.598(0.080)	0.618(0.075)	$a^{\#}$, $b^{\#}$, $c^{\#}$, $d^{\#}$, i*, j*
	0.663	0.632	0.623	0.616	0.628	
CTV O2	0.630(0.059)	0.666(0.058)	0.637(0.055)	0.625(0.048)	0.644(0.063)	a*, e*, f*, g*
	0.627	0.678	0.634	0.629	0.631	
CTV O3	0.641(0.062)	0.668(0.078)	0.673(0.060)	0.636(0.059)	0.671(0.076)	a*, b*, d*, $f^{\#}$, $h^{\#}$, $j^{\#}$
	0.648	0.666	0.665	0.659	0.674	
CTV O4	0.623(0.050)	0.636(0.052)	0.625(0.052)	0.653(0.041)	0.632(0.060)	c*, f*, h*, j
	0.632	0.634	0.627	0.650	0.640	
CTV O5	0.600(0.078)	0.610(0.093)	0.601(0.083)	0.591(0.090)	0.644(0.061)	$d^{\#}$, $f^{\#}$, $g^{\#}$, i*, $j^{\#}$
	0.612	0.637	0.600	0.559	0.652	
ρ	$k^{\#}$, $m^{\#}$, $n^{\#}$, q*, r*, s*	k*, l*, p^*, $q^{\#}$, r*, $s^{\#}$	k*, l*, o*, q^*, r*, s^*	$l^{\#}$, m*, p*, $q^{\#}$, $s^{\#}$, $t^{\#}$	l*, o*, r*, s^*	

*Statistical significance ($\rho < 0.05$) is reported between couples from paired t– test*and wilcoxon signed-rank test$^{\#}$;*

a – Plan O1 vs Plan O2, b –Plan O1 vsPlan O3, c–Plan O1 vsPlan O4, d –Plan O1 vsPlan O5, e –Plan O2 vsPlan O3, f –Plan O2 vsPlan O4, g –Plan O2 vsPlan O5, h –Plan O3 vsPlan O4, i–Plan O3 vsPlan O5, j –Plan O4 vsPlan O5

k– CTV O1 vs CTV O2, l – CTV O1 vs CTV O3, m – CTV O1 vs CTV O4, n – CTV O1 vs CTV O5, o – CTV O2 vs CTV O3, p – CTV O2 vs CTV O4, q – CTV O2 vs CTV O5, r – CTV O3 vs CTV O4, s – CTV O3 vs CTV O5, t – CTV O4 vs CTV O5

Table 11:
Mean (SD) and median of overdose volume index (OI) resulted from analysis of 500 evaluations of CTV of 5 observers on 20 patients and 5 plans of each observer for graphically optimized plans

	Overdose volume Index (OI)					
	Plan O1	**Plan O2**	**Plan O3**	**Plan O4**	**Plan O5**	**ρ**
CTV O1	0.072 (0.010) 0.072	0.071 (0.011) 0.070	0.072 (0.011) 0.071	0.069 (0.009) 0.068	0.072 (0.011) 0.073	c*, f*
CTV O2	0.067 (0.010) 0.067	0.070 (0.009) 0.068	0.068 (0.008) 0.067	0.067 (0.008) 0.066	0.069 (0.009) 0.067	a*, e*, f*, h*
CTV O3	0.065 (0.010) 0.067	0.067 (0.010) 0.068	0.068 (0.008) 0.067	0.065 (0.009) 0.066	0.067 (0.010) 0.068	a*, b*, d*, f*, h*
CTV O4	0.066 (0.010) 0.068	0.068 (0.010) 0.067	0.067 (0.009) 0.068	0.069 (0.009) 0.069	0.068 (0.010) 0.069	c*
CTV O5	0.069 (0.010) 0.070	0.071 (0.010) 0.071	0.070(0.009) 0.073	0.069 (0.009) 0.071	0.074 (0.011) 0.076	d*, f*, $h^{\#}$, $j^{\#}$
ρ	k*, l*, m*, o*, s*, t*	l*, m*, o*, p*, s*, t*	k*, l*, $m^{\#}$, $s^{\#}$, $t^{\#}$	k*, l*, o*, p*, r*, s*	k*, l*, m*, o*, q*, s*, t*	

*Statistical significance ($\rho < 0.05$) is reported between couples from paired t– test*and wilcoxon signed-rank test$^{\#}$;*

a – Plan O1 vs Plan O2, b –Plan O1 vsPlan O3, c–Plan O1 vsPlan O4, d –Plan O1 vsPlan O5, e –Plan O2 vsPlan O3, f –Plan O2 vsPlan O4, g –Plan O2 vsPlan O5, h – Plan O3 vsPlan O4, i–Plan O3 vsPlan O5, j –Plan O4 vsPlan O5

k– CTV O1 vs CTV O2, l – CTV O1 vs CTV O3, m – CTV O1 vs CTV O4, n – CTV O1 vs CTV O5, o – CTV O2 vs CTV O3, p – CTV O2 vs CTV O4, q – CTV O2 vs CTV O5, r – CTV O3 vs CTV O4, s – CTV O3 vs CTV O5, t – CTV O4 vs CTV O5

Table 12:

Mean (SD) and median of external volume index (EI) resulted from analysis of 500 evaluations of CTV of 5 observers on 20 patients and 5 plans of each observer for graphically optimized plans

	External volume Index (EI)					
	Plan O1	**Plan O2**	**Plan O3**	**Plan O4**	**Plan O5**	**ρ**
CTV O1	0.255 (0.114)	0.341 (0.209)	0.369 (0.210)	0.359 (0.217)	0.314 (0.183)	a#, b#, c*, d#, e#,i#
	0.221	0.264	0.281	0.298	0.238	
CTV O2	0.200 (0.081)	0.217 (0.095)	0.258 (0.107)	0.254 (0.123)	0.221 (0.123)	b#, c#, e#, f#, i#, j#
	0.202	0.197	0.232	0.216	0.201	
CTV O3	0.140 (0.084)	0.160 (0.095)	0.173 (0.081)	0.188 (0.115)	0.154 (0.123)	b#, c#, f#, i#, j#
	0.120	0.128	0.153	0.154	0.130	
CTV O4	0.170 (0.083)	0.200 (0.103)	0.228 (0.112)	0.193 (0.071)	0.195 (0.135)	b#, e#, i#
	0.146	0.164	0.190	0.178	0.166	
CTV O5	0.281 (0.158)	0.326 (0.225)	0.351 (0.185)	0.356 (0.267)	0.272 (0.107)	b# ,c#, e#, i#, j#
	0.266	0.294	0.294	0.339	0.258	
ρ	k*, l#, m#, o#, p#, q#, s#, t#	k#, l#, m#, o*, q#, s#, t#	k#, l#, m#, o#, q#, r#, s#, t#	k#, l#, m#, o#, p#, q#, s#, t#	k#, l#, m#, o#, q#, s#, t#	

*Statistical significance ($\rho < 0.05$) is reported between couples from paired t– test*and wilcoxon signed-rank test#;*

a – Plan O1 vs Plan O2, b –Plan O1 vsPlan O3, c–Plan O1 vsPlan O4, d –Plan O1 vsPlan O5, e –Plan O2 vsPlan O3, f –Plan O2 vsPlan O4, g –Plan O2 vsPlan O5, h – Plan O3 vsPlan O4, i–Plan O3 vsPlan O5, j –Plan O4 vsPlan O5

k– CTV O1 vs CTV O2, l – CTV O1 vs CTV O3, m – CTV O1 vs CTV O4, n – CTV O1 vs CTV O5, o – CTV O2 vs CTV O3, p – CTV O2 vs CTV O4, q – CTV O2 vs CTV O5, r – CTV O3 vs CTV O4, s – CTV O3 vs CTV O5, t – CTV O4 vs CTV O5

Table 13:
Mean (SD) and median of plan quality index (PQI) resulted from analysis of 500 evaluations of CTV of 5 observers on 20 patients and 5 plans of each observer for graphically optimized plans

	Plan Quality Index (PQI)					
	Plan O1	**Plan O2**	**Plan O3**	**Plan O4**	**Plan O5**	**ρ**
CTV O1	2.26 (0.10)	2.21 (0.12)	2.19 (0.11)	2.20 (0.10)	2.21 (0.12)	a*, b*, c#, d*, i*
	2.26	2.23	2.20	2.24	2.24	
CTV O2	2.19 (0.13)	2.26 (0.11)	2.21 (0.11)	2.20 (0.08)	2.22 (0.12)	a*, e*, f*, g*
	2.20	2.26	2.20	2.20	2.22	
CTV O3	2.17 (0.11)	2.23 (0.14)	2.23 (0.11)	2.18 (0.10)	2.22 (0.13)	a*, b*, d*, f*, h*
	2.19	2.21	2.20	2.19	2.26	
CTV O4	2.15 (0.11)	2.19 (0.11)	2.17 (0.11)	2.22 (0.09)	2.17 (0.12)	a*, c*, f*, h*, j*
	2.17	2.18	2.15	2.19	2.16	
CTV O5	2.17 (0.14)	2.20 (0.14)	2.18 (0.12)	2.17 (0.12)	2.25 (0.11)	d*, f*, g*, i*, j*
	2.17	2.22	2.20	2.19	2.26	
ρ	k*, l*, m*, n*, p*	k*, o*, p*, q*, r*	l*, p*, q*, r*, s*	r*, t*	m*, n*, p*, q*, r*, t*	

*Statistical significance (ρ < 0.05) is reported between couples paired t– test*and wilcoxon signed-rank test#;*

a – Plan O1 vs Plan O2, b –Plan O1 vsPlan O3, c–Plan O1 vsPlan O4, d –Plan O1 vsPlan O5, e –Plan O2 vsPlan O3, f –Plan O2 vsPlan O4, g –Plan O2 vsPlan O5, h – Plan O3 vsPlan O4, i–Plan O3 vsPlan O5, j –Plan O4 vsPlan O5

k– CTV O1 vs CTV O2, l – CTV O1 vs CTV O3, m – CTV O1 vs CTV O4, n – CTV O1 vs CTV O5, o – CTV O2 vs CTV O3, p – CTV O2 vs CTV O4, q – CTV O2 vs CTV O5, r – CTV O3 vs CTV O4, s – CTV O3 vs CTV O5, t – CTV O4 vs CTV O5

Table 14: Mean relative standard deviation (in %) for CI and COIN for optimized treatment plans

Table 14 a) Plans made for CTV of all observers evaluated for CTV of any individual observer		
	Coverage Index (CI)	**Conformal Index (COIN)**
CTV O1	1.8	5.1
CTV O2	3.3	4.2
CTV O3	3.6	4.6
CTV O4	3.5	3.6
CTV O5	2.9	5.4
Table 14 b) Plans made for CTV of individual observer was evaluated for CTV of all observers		
	Coverage Index (CI)	**Conformal Index (COIN)**
Plan O1	5.7	5.0
Plan O2	4.1	7.1
Plan O3	4.0	7.0
Plan O4	4.0	6.9
Plan O5	4.9	5.7

Abbreviations:

CTV O1, CTV O2, CTV O3, CTV O4 and CTV O5 – Clinical target volume delineated by Observer 1, Observer 2, Observer 3, Observer 4 and Observer 5

Plan O1, Plan O2, Plan O3, Plan O4 and Plan O5 – Optimized plan made on CTV of Observer 1, Observer 2, Observer 3, Observer 4 and Observer 5

Table 15: Impact of CTV variability on dosimetric parameters for graphically optimized plans

	Min	Max	Median	Mean	SD
V_{100} (cm^3)	86.5	264.6	159.2	160.7	52.1
V_{150} (cm^3)	22.7	60.9	39.2	39.5	12.0
V_{200} (cm^3)	8.1	19.3	13.9	13.8	3.4
CI_{common} of V_{100}	0.51	0.83	0.70	0.70	0.09
TRAK (cGy at 1m)	0.18	0.36	0.26	0.27	0.05
CTV coverage with V_{100_common} (%)	54.4	87.3	72.9	73.1	8.1
CTV coverage with V_{100_pair} (%)	63.1	92.2	76.9	77.9	7.3

Abbreviations:

V_{100} – Volume of breast in cm^3 receiving prescription dose

V_{150} - Volume of breast in cm^3 receiving 150% of prescription dose

V_{200} - Volume of breast in cm^3 receiving 200% of prescription dose

CI_{common} – Conformity index (spatial concordance) among all observers

TRAK – Total reference air kerma in cGy at 1 meter

V_{100_common} – Common volume of prescription dose among plans of all observers

V_{100_pair} – Common volume of prescription dose among plans of pairs

The mean±SD % increase in prescription dose to obtain adequate coverage due to inter-observer CTV variation was 8.8±6.1%. After increasing the prescription dose for $Plan_{Modified}$ there was a significant decline (11.5%; $\rho<0.05$) in the mean±SD of dose homogeneity (DHI,0.665±0.7), whereas a significant ($\rho<0.05$) increase of 10.3%, 53.4% and 29.3% in mean V_{100} (178.4±60.6cm^3), V_{150} (61.1±28.8cm^3) and V_{200} (17.9±5.8cm^3) respectively. This also yielded an improvement in the mean COIN (1.8% to 3.7%) for all observers. Among all $Plan_{Modified}$, the increase in the V_{150} and V_{200} beyond recommended values of RTOG0413 was observed for only CTV's larger than 180 cm^3.

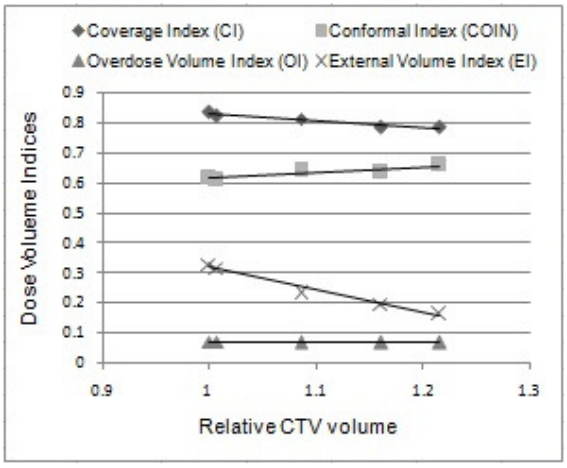


Figure 16: Plot between mean relative CTV volume among observers and mean dose volume indices.

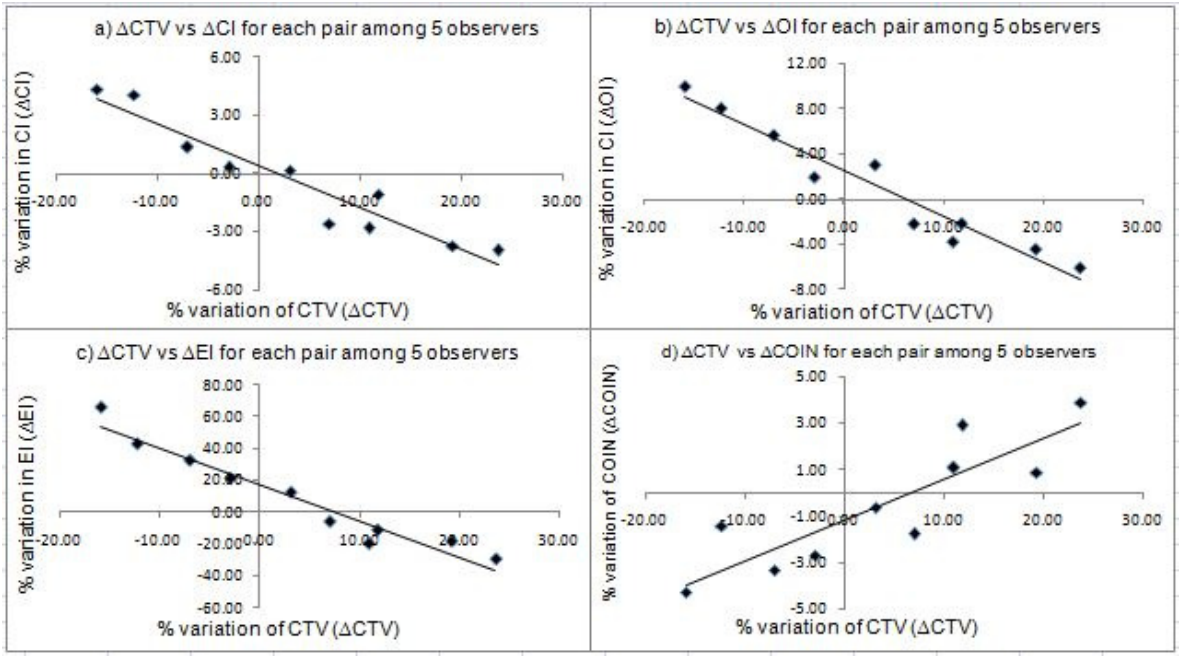


Figure 17: Plot between the mean % variation in the CTV volume of each pair among 5 observers with a) mean % variation in CI, b) mean % variation in OI, c) mean % variation in EI, d) mean % variation in COIN

4.4 Discussions:

Accuracy in target volume delineation is a crucial step in implementation of conformal radiotherapy [124]. In brachytherapy, there is no additional safety margin in the form of planning target volume. Moreover, as 3D conformal brachytherapy offers steep dose gradient around the CTV, the errors in target delineation will likely have an adverse impact on dosimetry and patient outcome. We have studied the inter-observer variation of target volume and demonstrated its impact on the variation of active dwell positions among plans of 5 different observers [126]. Out of 309 implanted catheters 23% showed a variation of more than 1 cm in the active dwell positions. Impact of inter-observer variation on the irradiated volume and TRAK

among all the observers for geometrically optimized plans was also reported. Literature search revealed limited studies on inter-observer variations of target volume delineation for partial breast brachytherapy and highlights the need for further evaluation [101, 126]. However, no work has been published on the dosimetric impact of such variations on dose volume parameters. This study is the first of its kind to report detailed dosimetric analysis of graphically optimized plans of all observers and the impact of the variation in the dose volume indices due to contouring heterogeneity.

Li XA et al [125] investigated the variability of target and organs at risk (OAR's) delineation for breast cancer radiotherapy for 9 observers on 3 patients planned for 3D conformal radiotherapy. They found substantial variability in target and OAR's delineation between the observers. Even though they observed no significant impact on dose coverage of PTV, the dosimetric variation in OAR's was substantial. Another study by Kosztyla R et al [70] reported the dosimetric consequences of seroma contour variability in APBI for external beam radiotherapy. They demonstrated median spatial concordance of 0.516 for seroma volume among three observers in 21 patients. However, they observed that planning margins provided adequate dose coverage of the seroma despite contouring variability of the PTV. In the last chapter we found the median concordance of 0.56 for the LC for MIB based APBI [126].

At our centre, for each patient, the placement of catheters was done at the time of the surgery after confirming the favorable report on frozen section evaluation of the primary and the lymph node. The lumpectomy surgery included the removal of the tumor with 1 cm margin, therefore 1 cm further margin beyond the cavity was considered safe for the CTV delineation [126]. GEC ESTRO breast cancer working

group (II) had recommended the total safety margins of 2 cm for CTV in all six directions including surgical resection margins around the tumor for the cases of open cavity surgery [123]. We had reported better spatial concordance of CTV on post implant planning CT images for MIB when compared with the only published study by Major et al [101]. Delineation of cavity was easier due to presence of seroma during the immediate post op period after open cavity surgery [119]. Further improvement in the delineation process could be achieved by utilizing other imaging modalities [magnetic resonance imaging (MRI), utrasonography (USG) etc.] for patients having poor visualization on CT images [133-137]. Reduction in the inter-observer variation and improvement in consistency in target delineation was reported for breast cancer patients using MRI along with CT imaging [133-136]. Patients with poor clarity of seroma in CT images and dense breast parenchyma showed improvement in inter-observer delineation consistency with USG imaging [137].

Our work demonstrated a significant impact in DVI's for brachytherapy plans among all five observers due to inter-observer variation in CTV volumes. Larger variability in all DVI's were observed, when a plan made for the CTV of individual observer was evaluated for the CTV of rest of the observers. Inter-observer variability showed highest impact on external volume index (EI). This was due to the impact of contour variability for graphically optimized plans where prescription isodose was optimized interactively to improve coverage of CTV. A change in the CTV contours due to the inter-observer variations resulted in greater differences in the volume of normal breast outside the CTV receiving doses equal to or greater than prescription dose.

The PQI used in the present work provides assessment of overall quality of treatment plans. As expected, the plans of each observer when evaluated for their own CTV had the highest PQI of ≥ 2.22 and comparable with previously published study [119].

This study showed that for increase of RCV among observers, there was a sharp relative decrease of EI compared to CI which was due to larger volume of CTV had relatively smaller volume of prescription dose outside CTV. Thus larger volume CTV had poorer CI but better COIN. Similar findings were observed for ΔCTV for each pair with significant correlation for variation in DVI's.

In our study we observed that even though an increase in the prescription dose caused a global expansion of the isodoses, it did not lead to unacceptable escalation of the V_{150} and V_{200} especially for patients with a CTV < $180cm^3$. The limitation of our work is that we did not investigate the feasibility of additional margins required to counteract the dosimetric variation due to uncertainties in CTV delineation. Tanderup et al [138] reported that for intracavitary brachytherapy it is possible to account for the PTV margins selectively in the longitudinal directions along the applicators to expand the dose distribution; however applying margins in the radial direction would cause dose escalation of target and OAR and therefore should be avoided. For interstitial breast brachytherapy, Resch et al [139] also demonstrated that imposing a lateral margin would escalate the dose in the central part of the target by 30 - 40% of mean central dose. Margins in the direction of the catheters are suggested by Das and Thomadsen for multi-catheter breast brachytherapy to account for the uncertainty due to shifts in the catheters with respect to target in the book by Wazer et al [140]. In our work we observed that the poor CTV coverage due to inter-observer variation in

delineation may be compensated with the increase in prescription dose when the CTV volume < 180 cm^3at the cost of DHI.

In this study we observed a 19% and 12.5% increase of mean V_{100} and TRAK respectively for graphically optimized plans when compared to geometrically optimized plans. Geometrical optimization utilizes only the geometry of the implant during optimization to homogenize dose distribution; therefore the spatial concordance of V_{100} is expected to vary only as result of a difference in the active source positions among various plans. However, in graphical optimization, the isodose volume was spatially modified to improve the conformity of individual target volume of observers apart from the variation in active source positions. Thus we observed a reduction of 7% of spatial concordance (CI_{common}) of V_{100} in graphical optimized plans when compared with geometrically optimized plans, which was due to the interobserver CTV variations.

The variability in target delineation resulted in variability of DVI's. Graphical optimization may have added some variability on dosimetric indices during the optimization process. To minimize this variability, plans were optimized by a single planner and also the dose homogeneity index was kept consistent (0.75) for all the plans. The limitation of the present study was that we did not investigated intra-observer variability during graphical optimization. Another limitation was that we did not investigate the dosimetric impact of inter-observer variations for the OARs. Skin and ribs may have the maximum dosimetic impact of inter-observer variability due to their proximity to the target. For our study skin doses was minimized by restricting the source positions within 0.5 cm of skin surface and further optimization. Every effort was made to also limit dose to the ribs.

4.5 Conclusion:

Inter-observer variation in delineation of CTV showed an impact on the source positions along catheters and statistically significant impact on the dose volume indices. Variations of <12% were observed for mean CI, OI and COIN. Inter-observer variation in delineation of CTV showed significant dosimetric impact with mean CTV coverage of 73.1% and 77.9% by common and paired prescription dose volume respectively among all observers. The prescription dose may be increased to counteract the decrease in dosimetric coverage at the cost of DHI for CTV <180cm^3.

*** *Publication:*** *This chapter is reproduced from the following publication which is a research article arises from the present thesis.*

Upreti RR, Budrukkar A, Upreti U, Wadasadawala T, Misra S, Gurrum L, Pathak R, Deshpande DD. "Impact of inter-obse rver variations in target volume delineation on dose volume indices for accelerated partial breast irradiation with multicatheter interstitial brachytherapy". Radiotherapy and Oncology; 2018:129; 173-179.

Chapter 5

Change in target volume during the course of brachytherapy treatment

5.1 Introduction

Treatment of breast cancer by APBI using MIB is established as an alternative treatment option to whole breast radiotherapy for selected patients [30-39]. After breast conservation surgery (BCS), when the surgery is performed with open cavity technique there is collection seroma in the surgical cavity [123,141,142]. Seroma cavity is known to show temporal changes during breast conserving therapy [143]. This may result in variation in the target volume during the course of treatment. In partial breast treatment using intraoperative, open cavity technique of MIB, the duration of brachytherapy treatment is generally 7-10 days, which also leads to accumulation of seroma and subsequent variation in volume [144]. Seroma formation after closed cavity technique is rarity [145].

In the recent years interfraction volumetric changes in target volume during the course of multilumen balloon brachytherapy (MLB) was reported for APBI [97-99]. Inter-fraction variation for the intraoperative breast implants utilizing radiograph based planning for APBI was investigated earlier at our institute [144], however only variations in catheter lengths during the course of treatment were reported. To our best knowledge, no published data is available for the inter-fraction changes of LC and CTV for intraoperative breast implants using open cavity technique for APBI and their subsequent impact on the dosimetric outcome.

We had transition from X-ray based brachytherapy to CT based planning for 3D partial breast brachytherapy in late 2005 [59] and have reported excellent local control rate and cosmesis with long term follow up [36]. The present study was carried out to quantify the interfraction changes in LC and CTV during the course of APBI and to quantify its impact on implant dosimetry using dose volume indices.

5.2 Materials and methods:

5.2.1 Patient Selection and Implant Technique:

Twenty two breast cancer parents treated with APBI using high dose rate (HDR) interstitial brachytherapy were selected for this study. Patients fulfilling the selection criteria for partial breast brachytherapy were considered for radical intraoperative implant. After the breast conserving surgery basic histopathological features were confirmed on the frozen section. The tumour bed was marked with radio-opaque clips placed at the borders and in the centre of the posterior wall of the lumpectomy cavity. Flexible nylon catheters were placed and guided through stainless steel needles using free hand insertion in multiple planes following Paris system.

5.2.2 Planning and Dosimetry:

Axial CT images were acquired (CT1) of the implanted region for each patient with 0.3 cm slice thickness on Somatom Emotion (Siemens Medical Systems, Germany) before start of the treatment. Images were exported to Oncentra v 4.3 brachytherapy treatment planning system (Elekta AB, Stockholm,Sweden).

The lumpectomy cavity (LC) was delineated on axial CT scans inclusive of the walls of cavity**,** seroma, air and radio-opaque clips. Clinical target volume (CTV) was drawn by uniform volume expansion with 1cm around the LC. Aim of the CTV was to obtain 2 cm margin from the primary tumor. As the surgery included removal of the tumor with 1 cm margin, 1cm further margin beyond the cavity was considered. However as the final histopathology was not available at the time of implantation, actual microscopic margins which were available after final histopathology report varied from 1 – 2 cm. CTV was edited form chest wall and 0.5 cm from the skin

surface. The air inside the lumpectomy cavity and ipsilateral breast was also delineated. Reconstruction of catheters was carried out in multi planar reconstructed images. Active source loading was obtained with a margin of 0.5 cm over CTV for each tube. The dose was normalized at basal dose points using Paris system. Initial plan was optimized geometrically on volume and prescribed on 85% of the mean basal dose. The plan was further optimized interactively using graphical optimization tool for optimum target coverage and dose homogeneity which yielded final plan P_{CT1}. While generating the optimal plan the recommendations of National Surgical Adjuvant Breast and Bowel Project (NSABP) B39/ Radiation Therapy Oncology Group (RTOG) protocol 0413 were followed to limit the doses to ipsilateral breast [129]. As per RTOG protocol the volume of ipsilateral breast receiving 1.5 times (V_{150}) and two times (V_{200}) of prescription dose was restricted to 70 cm^3 and 20 cm^3 respectively. The treatment was started on day 3 - 4 after placement of catheters. The duration of 3 - 4 days was considered optimal for healing of the surgical scar and post-op edema to settle. A dose of 3.4 Gy per fraction was prescribed using HDR technique using Ir-192 source. Total 10 fractions with 2 fractions daily were delivered to all patients. The final histopathology report was made available before the 5^{th} fraction to confirm the suitability for APBI.

The second CT scan was repeated on the last day of treatment. Median time from surgery to CT imaging for treatment planning (CT1) and prior to last fraction (CT2) was 2 days and 9 days respectively. Lumpectomy cavity, CTV and ipsilateral breast were contoured on the new CT dataset (CT2) by one of the co-authors for all cases. The delineation process may also have interobserver variation which was reported for partial breast brachytherapy with open cavity technique [101, 126]. To

minimize the subjective uncertainty, delineation of all patients was carried out by a single radiation oncologist using most appropriate and consistent window level and width setting. The intraobserver variation in the delineation was estimated by repeated contouring of five randomly selected patients amongst the twenty two in the study, with a time interval of more than 2 months.

Figure 18 (a) and figure 18 (b) represents the change in volume of seroma filled LC between the first day and the last day of treatment. All the catheters were reconstructed again in the new CT images. The source activity, source loading pattern and dwell times of each source positions of the brachytherapy plan P_{CT1} was then manually translated to the reconstructed catheters of new CT dataset (CT2). This resulted in plan $P_{CT2.}$ Care was taken to avoid all possible manual errors in translating the dwell positions, dwell times of each positions and the source activity. The total treatment time was verified with the original plan.

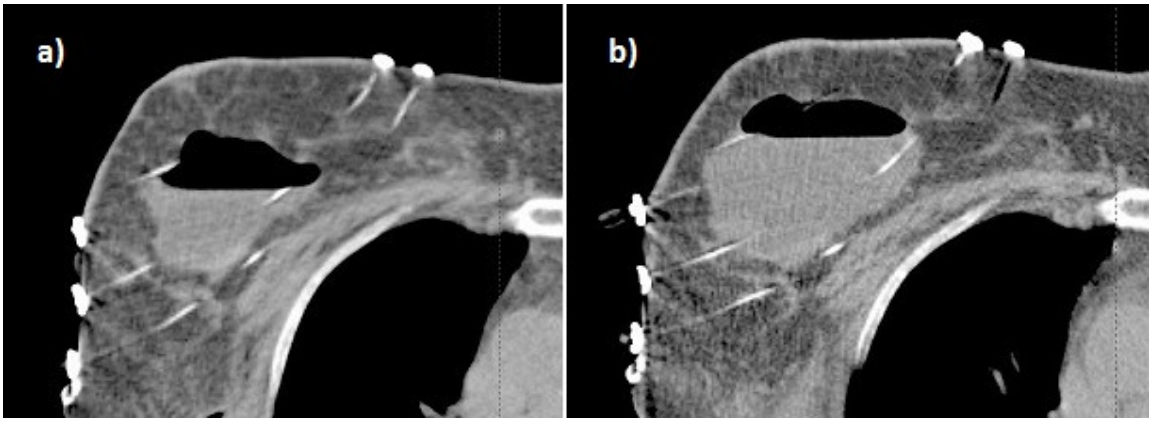


Figure 18: *Figure demonstrating the change in volume of seroma filled lumpectomy cavity during the first day (Figure 18 a) and the last day of treatment (Figure 18 b).*

5.2.3 Plan evaluation and comparison:

Initial plan P_{CT1}, generated on CT1 and the other plan created on the CT2 data set (P_{CT2}) were evaluated and compared using dose volume indices (CI, DHI,EI,OI and COIN) which are described in Table 5 a) [130, 131]. The V90, V95, D90 and D95 of CTV volume were also quantified. V90 and V95 of CTV represents the percentage of the CTV volume receiving more than 90% and 95% of the prescribed dose and D90 and D95 are the minimum doses (in percentage of the prescribed dose) encompassing 90% and 95% of the CTV volume. The mean of absolute difference for all parameters was also computed. The correlation between change of air volume inside the lumpectomy cavity and change of LC and CTV volume was also evaluated.

5.2.4 Statistical analysis:

Statistical Package for Social Sciences (SPSS version 20.0, IBM, Chicago) was used for analysis. The normality of the data was checked using Shapiro-Wilk test. T-test was used for pared samples comparisons. Wilcoxon signed-rank test was used for those samples in which the data deviates from normal distribution. Spearman correlation was carried out between variation of air volume in LC with change in LC and CTV volume.

5.3 Results:

The mean±SD volume of lumpectomy cavity was 78.5 ± 40.7cm^3 (range 30.9 – 194.0cm^3) for P_{CT1} while it was 84.7 ± 50.1 cm^3 (range 24.5 – 218.7 cm^3, $\rho = 0.110$) for P_{CT2}. The same for the volume of CTV was 156.4 ± 69.0 cm^3 (range 73.1 – 340.1 cm^3) for P_{CT1} and165.7 ± 82.8 cm^3 (range 61.3 – 382.2 cm^3 $\rho = 0.149$) for $P_{CT2.}$ The mean (SD) of absolute pair wise differences in LC and CTV volume for all cases was

10.0 (11.4) cm^3 and 21.4 (15.6) cm^3 respectively which was > 11% and 13% of their respective mean absolute volumes. The mean ± SD change in air volume inside the LC was 6.5 ± 3.1 cm^3 between P_{CT1} and P_{CT2}. Insignificant correlation between change of air volume in LC with change of LC volume ($r = 0.36$, $\rho = 0.10$) and CTV volumes ($r = 0.132$, $\rho = 0.559$) was observed.

Table 16: Change in volumes of Lumpectomy Cavity (LC) and Clinical Target Volume (CTV) between the first and last day of treatment.

Change in volume (%)	**Number of patient, n (%)**	
	LC	**CTV**
≥ -10	2 (9.1)	5 (22.7)
≥ -10, < 0	7 (31.8)	2 (9.1)
≥ 0, < 10	3 (13.6)	6 (27.3)
≥ 10, < 20	7 (31.8)	7 (31.8)
≥ 20, < 30	1 (4.5)	1 (4.5)
≥ 30	2 (9.1)	1 (4.5)

Variations in the LC and CTV volume are shown in Table 16. The mean±SD intraobserver variation was found to be 4.8±1.7 % for the delineation of LC and 4.3±2.6 % for the CTV. Volume increase of over 10% was observed in 10 cases (45.5%) for LC, however it was found in 9 cases (40.9%) for CTV. Increases by >10 to ≤20%, >20 to ≤30%, and >30% were observed in 7, 1, and 2 cases respectively for LC, however for CTV the similar increase was seen in 7, 1 and 1 cases respectively.

Greatest increase in the LC and CTV volumes was 35.5 % and 34.4 % respectively. A volume decrease of 10% or more was observed in 2 (9.1%) and 5 (22.7%) cases for LC and CTV with maximum decrease of 20% and 17.6% respectively.

Dose volume indices of CTV for both the plan P_{CT1} and P_{CT2} are summarized in the Table 17 and Table 18. Mean absolute variations of CI and COIN for CTV are given in Table 19. The cases with increase in CTV volume, mean CI and COIN was decreased significantly ($p< 0.05$) by 8.4% (CI = 0.752, SD = 0.073) and 5.5% (COIN = 0.598, SD = 0.056) in plan $P_{CT2}$when compared to plan P_{CT1} (CI = 0.821, SD = 0.078) and (COIN = 0.633, SD = 0.060) respectively. The cases with shrinkage of CTV showed significant decrease ($p= 0.001$) of 13.5% in COIN. The significant ($p= 0.004$) decrease of 12.3% in EI was found in the cases with increase in CTV volume, however for the cases with decrease in CTV showed 45% ($p= 0.003$) increase in EI. Variations in other indices were found insignificant. Overall 22 cases showed significant decrease of 5.8% and 8.1% in mean CI and COIN. Pair wise comparison showed 3.5% and 12.1% difference in mean absolute DHI and OI in $P_{CT2}$for all 22 cases. Significant decrease ($\rho < 0.05$) of 4.1%, 5.1%, 6.7% and 6.4% was also observed in mean values of V90, V95, D90 and D95 of CTV respectively for all 22 cases. Variation of <1% in the mean (SD) volume of prescription dose ($V_{100\%}$) in both the plans was observed, however found insignificant. Absolute variation of >5% in CI and COIN of CTV was found in 14 (63.6%) and 17 (77.3%) cases respectively.

Table 17: Mean (standard deviation) of CTV volume and dose volume indices [$] for plan P_{CT1} and P_{CT2}

n		CTV Volume (cm3)	CI CTV	DHI	OI	EI (cm^3)	COIN[^]	$V_{100\%}$ (cm^3)
Overall n = 22	Plan P_{CT1}	156.4 (69.0)	0.824 (0.073)	0.751 (0.042)	0.071 (0.018)	35.31 (8.58)	0.632 (0.052)	161.11 (51.80)
	Plan P_{CT2}	165.7 (82.8)	0.776 (0.081)	0.737 (0.052)	0.071 (0.021)	37.26 (14.26)	0.581 (0.062)	160.93 (52.09)
	Pair wise absolute difference (%)	13.2 (6.7)	7.0 (4.5)	3.5 (2.5)	12.1 (7.5)	24.6 (20.5)	8.5 (6.2)	0.85 (0.73)
	p value	0.149[#]	0.000[*]	0.031[#]	0.113[#]	0.428[*]	0.000[*]	0.625[*]
Increase in CTV volume n = 15	Plan P_{CT1}	163.5 (73.5)	0.821 (0.078)	0.757 (0.034)	0.071 (0.019)	35.73 (8.5)	0.633 (0.06)	166.51 (53.09)
	Plan P_{CT2}	186.0 (87.5)	0.752 (0.073)	0.746 (0.042)	0.069 (0.019)	31.35 (8.8)	0.598 (0.056)	166.87 (53.5)
	Pair wise absolute difference (%)	13.0 (7.9)	8.3 (4.6)	3.1 (1.7)	10.8 (6.0)	15.2 (12.7)	6.1 (4.3)	0.79 (0.56)
	p value	0.001[#]	0.000[*]	0.099[#]	0.286[*]	0.004[*]	0.002[*]	0.440[*]
Decrease in CTV volume n = 7	Plan P_{CT1}	141.1 (60.5)	0.831 (0.067)	0.739 (0.057)	0.072 (0.018)	34.42 (9.38)	0.629 (0.034)	149.53 (50.83)
	Plan P_{CT2}	122.2 (53.6)	0.827 (0.079)	0.717 (0.069)	0.075 (0.033)	49.9 (15.99)	0.544 (0.062)	148.20 (50.41)
	Pair wise absolute difference (%)	13.3 (3.3)	4.3 (2.3)	4.3 (3.7)	16.9 (10.0)	44.4 (20.0)	12.7 (6.9)	1.0 (1.1)
	p value	0.001[*]	0.793[*]	0.176[#]	0.799[#]	0.003[*]	0.001[*]	0.109[*]

** T-test for paired samples having normal distribution*

 # Wilcoxon signed-rank test for related samples which deviates from normal distribution

Abbreviations:

LC – Lumpectomy cavity,

CTV – Clinical target volume,

CI – Coverage index,

DHI – Dose homogeneity index,

OI – Overdose volume index,

EI – External volume index,

COIN – Conformal index,

$V_{100\%}$ – Volume of normal breast receiving prescription dose

Plan (P_{CT1}) – Optimal 3D plan on CT1 images acquired for treatment planning,

Plan (P_{CT2}) – Resulted treatment plan when plan (P_{CT1}) manually reproduced on the 2nd CT data set (CT2) acquired prior to last fraction.

[$] *Dose volume Indices - Meertens, H et al, Brachytherapy from radium to optimization. Nucletron International 1994;300-306.*

[^] *Conformal Index - Baltas D et al, Int J Radiat Oncol Biol Phys1998;40:515–524.*

Table 18:

Dose volume parameters of CTV for plan P_{CT1} and P_{CT2} (mean, standard deviation)

Dose Volume parameter	Plan P_{CT1}	Plan P_{CT2}	Pair wise absolute difference (%)	p value*
V90 (%)	88.3 (6.7)	84.2 (7.4)	5.5	0.000
V95 (%)	85.6 (7.1)	80.5 (7.7)	6.5	0.000
D90 (%)	86.8 (12.5)	80.1 (12.9)	9.4	0.001
D95 (%)	75.9 (13.5)	69.5 (13.8)	11.0	0.003

** T-test for paired samples*

Abbreviations:

V90 – % of the CTV volume receiving more than 90% of the prescription dose

V95 – % of the CTV volume receiving more than 95% of the prescription dose

D90 – Minimum dose (in % of the prescription dose) encompassing 90% of the CTV volume

D95 – Minimum dose (in % of the prescription dose) encompassing 90% of the CTV volume

Plan (P_{CT1}) – Optimal 3D plan on CT1 images acquired for treatment planning,

Plan (P_{CT2}) – Resulted treatment plan when plan (P_{CT1}) manually reproduced on the 2^{nd} CT data set (CT2) acquired prior to last fraction.

Table 19:

Mean absolute variation in Coverage Index (CI) and Conformal Index (COIN) of Clinical Target Volume (CTV)

Variation (%)	CI n (%)	COIN n (%)
> 0, ≤ 5	8 (36.4)	5 (22.7)
> 5, ≤ 10	9 (40.9)	11 (50)
> 10	5 (22.7)	6 (27.3)

Abbreviations:

LC – Lumpectomy cavity,

CTV – Clinical target volume,

CI – Coverage Index,

COIN – Conformal Index

5.4 Discussion

Multicatheter interstitial brachytherapy is one of the time-tested techniques of APBI with longest follow up [30 - 39]. APBI using intraoperative MIB was initiated at our institution in May 2000 [120]. Our centre is one of the few centres in the world which considers placement of catheters at the time of the surgery. This technique has great advantage of direct visualization of the tumour bed and placement of catheters which poses a problem when APBI is considered postoperatively. Also delineation of cavity on CT scan is superior due to presence of seroma which may not be the case in closed cavity technique or postoperative brachytherapy [123,126,145]. However this

requires excellent coordination between surgical team, radiation oncologist, pathologist and medical physicist. From patients' point of view this treatment has a great advantage as the entire surgery and radiation is completed in 10 days from the surgery. Many centres face constraints for using this technique due to unavailability of histopathology report in stipulated time. However in our centre all patients had frozen section evaluation of the primary and lymph node status before proceeding for placement of catheters. Placement of implant was done only after confirming the favourable report. In addition, final histopathology was made available before the 5^{th} fraction which was generally given on 5 - 7^{th} day after the surgery. The results of our technique have already been published [36,119,127]. For intraoperative multicatheter partial breast brachytherapy, changes in the lumpectomy cavity are likely to occur during the immediate post op period, which is a matter of concern and investigated in the present study.

Accumulation of seroma and its dosimetric impact during APBI using multilumen balloon brachytherapy (MLB) was investigated by Bhatt et al [97-99]. Serial aspirations of the vacuum port of the MLB catheter were performed at the time of initial CT simulation and then before each treatment fraction using Ir-192 HDR brachytherapy treatment which was delivered to a dose of 34Gy in 10 fractions over 5 consecutive treatment days. They had observed variable pattern of development in seroma accumulation with no discernible predictors of occurrence [97]. Impact of interfraction seroma collection on breast brachytherapy was investigated by Bhatt et al using mathematical model with symmetric expansions of 1.0 mm (0-9 mm) increments around the balloon surface to simulate "Virtual Seroma" (VS) accumulation and re-planning for two balloon volumes [98]. They had demonstrated

that accumulation of seroma can significantly impact the PTV dosimetry. In another retrospective study, Bhatt et al investigated variation of PTV dosimetry as a factor of the seroma volume [99]. They had re-planned the cases with and without accounting for seroma and reported a considerable negative impact on PTV dosimetry resulting in 2.45% decrease in PTV coverage by 90% (V90) isodose line for every 1 cc of accumulated seroma. Their findings cannot be directly correlated with our results due to the difference in the APBI technique and also the methodology was not done in real time in patients during treatment. In the current study, we have observed 5.8% and 8.1% decrease in the mean coverage and conformity of the CTV respectively. Kuo H et al [100] acquired CT scan on every day (one simulation CT and five daily CT) for all 7 studied cases of multilumen balloon brachytherapy and observed < 1% variation in V90 and V95 of PTV volume. However they had maintained the seroma volume within 2% or 2 cm^3 of the PTV volume by ensuring the conformance of balloon to the resection cavity using pretreatment aspiration.

Interfraction variation for intraoperative breast implants was earlier studied by repeating radiographs and CT scans on the alternate days for fourteen patients at our institute [144]. However the study was limited to documentation of the variations in the catheter length during the course of treatment. Out of 171 catheters studied in 14 patients, significant variation of more the 5 mm and 10 mm in catheter length were reported in 100 (58%) and 38 (22%) catheters respectively. However in the absence of CT based 3D brachytherapy the study was carried out using the conventional radiograph based planning where the variation in target volume during the treatment course was not investigated.

For the present study CT scan of all patients was re-acquired at last treatment fraction for investigating of maximum variations in the lumpectomy cavity and target volume. We had earlier investigated interobserver variability in the delineation for LC and CTV in the previous chapter [126]. Subjective uncertainties in structure delineation were kept minimal by assigning the segmentation work to a single radiation oncologist (co-author) and estimating intraobserver variation. Recently GEC ESTRO has recommended the total safety margins of 2 cm for CTV in all 6 directions including surgical resection margins around the tumour for the cases of open cavity surgery [123]. It was also recommended to have safety margin for CTV of at least 0.5 cm whenever surgical margins are larger than 2 cm [123]. In our centre the lumpectomy surgery included removal of the tumor with 1cm margin, therefore 1cm further margin beyond the cavity was considered safe for the CTV delineation. GEC ESTRO also recommends determination of the boundaries of lumpectomy cavity utilizing seroma and surgical clips. For the present study the visualization of seroma, air in cavity and surgical clips were used for the delineation of lumpectomy cavity.

The quantitative evaluation and the comparison of the implant dosimetry showed the significant decrease in the overall mean CI and COIN of CTV for 22 cases, however there was less than 1% absolute variation in the mean (SD) volume of prescription dose ($V_{100\%}$) in both the plans. The decrease in CI of CTV was found significant for the cases having increase in CTV volume. The observed variation in mean DHI could be due to minor changes in the inter catheter separation because of variations in the seroma filled LC volume or changes in patient posture while imaging or treatment. Care was taken to avoid any variation in the tube length inside the patient during entire course of treatment; also the patient posture was kept consistent

during CT imaging and all treatment fractions. However the variation in DHI in both group of patient with increasing and decreasing CTV was found insignificant. The limitation of the present work was that we did not investigate the minor changes in the inter-catheter separation which were non-specific and difficult to quantify.

Larger variations were observed in the pair wise estimation of mean absolute difference of EI in the present work which was found significant in both the groups consisting of increasing and decreasing volume of CTV. To maximize conformity in all cases, plan P_{CT1} was graphically optimized, therefore any small change in shape and size of CTV yielded greater variations in the volume of normal tissues beyond the target volume receiving dose larger than the prescription dose yielded larger absolute pair wise variation in EI.

Due to accumulation of seroma and air in cavity, we observed larger volume of CTV for intra-operative open cavity implant when compare with postoperative technique [59, 119]. The underdose in the anterior part of the CTV was accepted to avoid skin irradiation which contains only air in cavity. However it was previously reported that open cavity MIB having equivalent efficacy in the target coverage and homogeneity when compared to closed cavity technique [119].

Present study suggests to acquire a CT scan in the mid of treatment to assess the changes in the target volume. Adaptive treatment planning can be considered if the variation in the CTV volume is beyond the intra-observer variability of the target delineation.

5.5 Conclusion:

The change in the target volume during the course of APBI using intraoperative multicatheter interstitial brachytherapy after open cavity surgery was found patient specific and showed a significant impact on coverage and conformity.

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Chapter 6

Summary, conclusion and future directions

6.1 Summary and Conclusion:

In this thesis the uncertainties for 3D conformal brachytherapy specific to multi-catheter interstitial breast implants was investigated. Following are the summary and conclusions of this thesis.

The reconstruction errors, which leads to the geometrical uncertainty was found to be larger when the implant and catheter orientation are near to parallel with imaging plane. As the slice thickness decreases and angle of implanted catheters with respect to imaging plane increases, there was reduction in the uncertainties. Smallest slice thickness had the least reconstruction uncertainty.

APBI using radical breast brachytherapy involves the irradiation limited to partial breast volume, which necessitates the accurate target delineation. As the volume around tumor bed is at higher risk of tumor relapse if treatment is not adequate. Present work in the thesis found a significant delineation variability in LC and CTV intra-operative multi-catheter partial breast brachytherapy, which was significantly related to cavity visualization index (CVI). The relative standard deviation in target volume delineation for intra-operative MIB was found to be 11.7% (k=1). Patients having excellent visualization of lumpectomy cavity showed smaller delineation variability in CTV and lumpectomy cavity.

An inter-observer variation in the target delineation yielded the variations on the active dwell positions in catheters and therefore significant dosimetric impact was observed on dose volume indices. Graphically optimized conformal plans showed variations of up to 12 % in the mean dosimetric coverage and conformality of CTV. Delineation variability also yielded in the CTV coverage with 73.1% and 77.9%

common and paired prescription dose volume respectively among all observers. The mean RSD of 5.7% and 7.1% (k=1) in the dosimetric coverage and conformality respectively was found due to inter-observer delineation variability.

The post-operative changes in the tumour bed after intra-operative placement of brachytherapy catheters are due to accumulation of seroma during breast conservation therapy. These temporal changes caused the patient specific variation in the CTV during APBI using multi-catheter partial breast brachytherapy and yielded a significant reduction of 5.8% and 8.1% in mean CTV coverage and conformity.

6.2 Future directions:

The present work showed that geometrical uncertainties can be minimizes by reducing scan thickness and increasing the orientation angle of the implant from imaging plane. Reconstruction errors may lead to the variations in the implant dosimetry. A systematic study simulating systematic errors and their impact on the implant dosimetry could be a subject of future investigation. As the reconstruction errors in the breast brachytherapy implants are also influenced with the breathing motion of the patient, a study addressing the errors due to breathing motion could be a subject of the future work.

The work carried out in the present thesis showed that even though the delineation process is standardized, there is a need of further investigation for minimizing the delineation uncertainty in those patients who has poor visibility of lumpectomy cavity. Few investigators reported superior consistency in target delineation and improvement in delineation variability when MRI imaging are added with CT and patients with dense breast parenchyma showed better visualization with

USG imaging. Role of other imaging modalities could be a subject of research for the further improvements in delineation process.

It was demonstrated that although increase in the prescription dose may be used to compensate for delineation variability for smaller target volumes (<180cm^3) at the cost of homogeneity for 3D conformal plans, however investigation of feasibility of additional margins to address dosimetric variation due to delineation variability could be a subject of investigation. Although margins in the radial directions of the catheters are not recommended in brachytherapy, margins along the catheters still can be applied.

The work in thesis demonstrated the patient specific variability in the target volume during APBI using multicatheter brachytherapy which was found to have significant impact on target coverage and conformality. Adaptive brachytherapy could be a subject of future research if the change in the target volume is larger than the intra-observer variability in target delineation.

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Original paper

Interobserver variations of target volume delineation and its impact on irradiated volume in accelerated partial breast irradiation with intraoperative interstitial breast implant

Ritu Raj Upreti, MSc, DipRP[1], Ashwini Budrukkar, MD[2], Tabassum Wadasadawala, MD[3], Shagun Misra, MD[2], Lavanya Gurram, MD[2], Rima Pathak, MD[2], Deepak D. Deshpande, PhD[1]

[1]Department of Medical Physics, Tata Memorial Hospital, Parel, Mumbai, [2] Department of Radiation Oncology, Tata Memorial Hospital, Parel, Mumbai,[3] Department of Radiation Oncology, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Navi Mumbai, India

Abstract

Purpose: To investigate the interobserver variations in delineation of lumpectomy cavity (LC) and clinical target volume (CTV), and its impact on irradiated volume in accelerated partial breast irradiation using intraoperative multicatheter brachytherapy.

Material and methods: Delineation of LC and CTV was done by five radiation oncologists on planning computed tomography (CT) scans of 20 patients with intraoperative interstitial breast implant. Cavity visualization index (CVI), four-point index ranging from (0 = poor) to (3 = excellent) was created and assigned by observers for each patient. In total, 200 contours for all observers and 100 treatment plans were evaluated. Spatial concordance (conformity index, CI_{common}, and CI_{gen}), average shift in the center of mass (COM), and ratio of maximum and minimum volumes (V_{max}/V_{min}) of LC and CTV were quantified among all observers and statistically analyzed. Variation in active dwell positions (0.5 cm step) for each catheter, total reference air kerma (TRAK), volume enclosed by prescription isodose ($V_{100\%}$) among observers and its spatial concordance were analyzed.

Results: The mean ± SD CI_{common} of LC and CTV was 0.54 ± 0.09, and 0.58 ± 0.08, respectively. Conformity index tends to increase, shift in COM and V_{max}/V_{min} decrease significantly ($p < 0.05$), as CVI increased. Out of total 309 catheters, 29.8% catheters had no change, 29.8% and 17.5% catheters had variations of 1 and 2 dwell positions (0.5 cm and 1 cm), respectively. 9.3% catheters shown variations ≥ 10 dwell positions (5 cm). The mean ± SD CI_{common} of $V_{100\%}$ was 0.75 ± 0.11. The mean observed V_{max}/V_{min} of prescription isodose and TRAK was 1.18 (range, 1.03 to 1.56) and 1.11 (range, 1.03 to 1.35), respectively.

Conclusions: Interobserver variability in delineation of target volume was found to be significantly related to CVI. Smaller variability was observed with excellent visualization of LC. Interobserver variations showed dosimetric impact on irradiation of breast tissue volume with prescription dose.

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Key words: APBI, breast cancer, cavity visualization, interobserver variation.

Purpose

Accelerated partial breast irradiation (APBI) for early stage breast cancer using multi-catheter interstitial brachytherapy (MIB) has shown promising early results for selected subgroup of patients [1,2,3,4,5,6,7,8,9]. The APBI technique offers overall reduction of treatment time to 1 week, compared to 3-6 weeks of standard whole breast radiation therapy due to the irradiation of confined target volume around the lumpectomy cavity (LC).

Conventional dosimetry of MIB for APBI was carried out using a set of localization radiographs, which limited the three-dimensional (3D) definition of the target volume, thereby resulting in larger irradiated volume [10,11]. During the last decade, 3D image based brachytherapy has evolved, which provided clinically realistic dosimetric information on patient anatomy [10,11,12,13,14,15].

Active source positions in 3D brachytherapy are loaded in the vicinity of the 3D defined target volumes. Hence,

Address for correspondence: Ritu Raj Upreti, MSc, DipRP, Department of Medical Physics, Tata Memorial Hospital, Dr. Ernest Borges Marg, Parel, Mumbai, India 400012, phone: +91 22 24112427, fax: +91 22 24146747, e-mail: rituraaj123@yahoo.com

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Brachytherapy

Impact of inter-observer variations in target volume delineation on dose volume indices for accelerated partial breast irradiation with multi-catheter interstitial brachytherapy

Ritu Raj Upreti [a,d,*], Ashwini Budrukkar [b], Udita Upreti [a], Tabassum Wadasadawala [c], Shagun Misra [b], Lavanya Gurram [b], Rima Pathak [b], Deepak D. Deshpande [a,d]

[a] Department of Medical Physics; [b] Department of Radiation Oncology, Tata Memorial Hospital; [c] Department of Radiation Oncology, Advanced Centre for Treatment, Research and Education in Cancer; and [d] Homi Bhabha National Institute, Training School Complex, Mumbai, India

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ABSTRACT

Purpose: To investigate dosimetric impact of inter-observer variation in clinical target volume(CTV) delineation for patients undergoing interstitial partial breast brachytherapy.
Methods: Five radiation oncologists delineated CTV in twenty patients who underwent multi-catheter partial breast brachytherapy. Five treatment plans for each patient were graphically optimized for CTV of all observers and evaluated using coverage index(CI), external volume index(EI), overdose volume index(OI) and conformal index(COIN). In addition, volume enclosed by prescription isodose(V_{100}), its spatial concordance(CI_{common}), mean coverage of all CTVs with common volume of prescription dose (V_{100_common}) and mean CTV coverage for all pairs of observer with common prescription volume of respective pairs(V_{100_pair}) were also computed.
Results: The mean ± standard deviation(SD) of CI and COIN ranged from 0.756 ± 0.076 to 0.840 ± 0.070 and 0.591 ± 0.090 to 0.673 ± 0.06 respectively. When a plan made for CTV of individual observer was evaluated on CTV of all observers, the maximum variations($\rho < 0.05$) in the mean CI,COIN,OI and EI were 10.6%,11.4%,10.6% and 72.7% respectively. The observed mean ± SD of V_{100}, CI_{common} of V_{100}, CTV coverage with V_{100_common} and V_{100_pair} was 160.7 ± 52.1, 0.70 ± 0.09, 73.1 ± 8.1% and 77.9 ± 7.3% respectively.
Conclusion: Inter-observer variation in delineation of CTV showed significant dosimetric impact with mean CTV coverage of 73.1% and 77.9% by common and paired prescription dose volume respectively among all observers.
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Conformal radiotherapy requires accurate delineation of target volume and inter-observer variation in delineation is a potential source of error in radiotherapy [1]. Accelerated partial breast irradiation(APBI) using multi-catheter interstitial brachytherapy(MIB) is established as an alternative to whole breast irradiation with excellent results for a selected subgroup of patients [2–7]. Three dimensional(3D) computed tomography(CT) based MIB allows conformal planning as it produces steep dose gradient beyond the target. Thus, inter-observer variation in target delineation is likely to have an impact on dosimetric and clinical outcomes. Studies evaluating dosimetric impact of inter-observer variability in target delineation have been conducted for APBI with external beam radiotherapy [8,9]. To the best of our knowledge, no published data exist on the dosimetric impact of inter-observer variation in target delineation for intraoperative breast implants. We have quantified inter-observer variation in delineation of lumpectomy cavity(LC) and clinical target volume(CTV) for intraoperative breast implants in our previous report [10]. The present study is carried out to investigate the impact of the inter-observer variation on dose volume indices(DVIs) for graphically optimized plans as an extension of our previous work.

Materials and methods

Patient selection and imaging

Twenty patients of early stage breast cancer satisfying the eligibility criteria for APBI (tumor size up to 3 cm, negative margins and pathologically negative axilla) were retrospectively included for the study.

The tumor bed was identified using 5 radio-opaque clips placed at the centre, superior, inferior, medial and lateral edges of the

* Corresponding author at: Department of Medical Physics, Tata Memorial Hospital, Dr. Ernest Borges Marg, Parel, Mumbai 400012, India.
E-mail address: upretir@tmc.gov.in (R.R. Upreti).

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Physics

Change of target volume and its dosimetric impact during the course of accelerated partial breast irradiation using intraoperative multicatheter interstitial brachytherapy after open cavity surgery

Ritu Raj Upreti[1,*], Ashwini Budrukkar[2], Udita Upreti[1], Shagun Misra[2], Tabassum Wadasadawala[3], Satish Kohle[1], Deepak D. Deshpande[1]

[1]*Department of Medical Physics, Tata Memorial Hospital, TMC, Parel, Mumbai, India*
[2]*Department of Radiation Oncology, Tata Memorial Hospital, TMC, Parel, Mumbai, India*
[3]*Department of Radiation Oncology, Advanced Centre for Treatment, Research and Education in Cancer, TMC, Kharghar, Navi Mumbai, India*

ABSTRACT

PURPOSE: To investigate the change of clinical target volume (CTV) and its dosimetric impact during the course of accelerated partial breast irradiation (APBI) using intraoperative multicatheter interstitial brachytherapy after open cavity surgery.

METHODS AND MATERIALS: Twenty-two patients of APBI with intraoperative placement of catheters underwent computed tomography scans for the treatment planning before the first (CT1) and the last (CT2) treatment fraction. Delineation of lumpectomy cavity and CTV was done consistently on both CT data sets by one of the coauthors. Optimum plan (P_{CT1}) was made on CT1. P_{CT1} was manually reproduced in CT2 which yielded plan P_{CT2}. Plans were compared using coverage index (CI), dose homogeneity index (DHI), external volume index (EI), overdose volume index (OI) and conformal index (COIN).

RESULTS: The mean ± SD volume of lumpectomy cavity and CTV was 78.5 ± 40.7 cm^3, 156.4 ± 69.0 cm^3 for P_{CT1}, and 84.7 ± 50.1 cm^3 ($p = 0.11$), 165.7 ± 82.8 cm^3 ($p = 0.15$) for P_{CT2}, respectively. CTV volume increase by ≥ 10% was observed in 9 cases however decrease of ≥10% was observed in 5 cases. Mean (SD) of absolute pairwise difference in CTV volume was found to be 13.2 (6.7) %. For cases with increase in CTV volume, significant ($p < 0.05$) decrease of 8.4%, 12.2%, and 5.5% was observed in CI, EI, and COIN of CTV respectively. However for cases with shrinkage of CTV, significant ($p = 0.004$) increase of 45% in EI was observed, whereas COIN reduced significantly ($p = 0.001$) by 13.5%. Overall 22 cases showed significant decrease of 5.8% and 8.1% in mean CI and COIN, respectively.

CONCLUSIONS: The change of CTV during the course of APBI using intraoperative multicatheter interstitial brachytherapy after open cavity surgery was found patient specific and showed a significant impact on coverage and conformity.

Keywords: Interfraction target variation; Multicatheter interstitial brachytherapy; Dose volume indices; Accelerated partial breast irradiation

Introduction

Treatment of early-stage breast cancer in selected subgroup of patients by accelerated partial breast irradiation (APBI) using multicatheter interstitial brachytherapy (MIB) is established as an alternative treatment option to whole-breast irradiation (1–8). After breast conservation surgery, when the surgery is performed with open cavity technique, there is collection seroma in the surgical cavity (9–11). Seroma cavity is known to show temporal changes during breast conserving therapy (12). This may result in

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* Corresponding author. Department of Medical Physics, Tata Memorial Hospital, Ernest Borges Marg, Parel, Mumbai, India 400012. Tel.: +91 22 24112427; fax: +91 22 24146747.

E-mail address: rituraaj123@yahoo.com (R.R. Upreti).

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INTER OBSERVER VARIATION IN DELINEATING LUMPECTOMY CAVITY AND CTV FOR PATIENTS UNDERGOING APBI USING INTRA-OPERATIVE IMPLANTS AND ITS IMPACT ON IMPLANT DOSIMETRY

Ritu Raj Upreti [a,*], Ashwini Budrukkar [b], Tabassum Wadasadawala [b], Shagun Mishra [b], Lavanya Naidu [b], Rima Pathak [b], Deepak D. Deshpande [a]

[a] *Department of Medical Physics, Tata Memorial Centre, Mumbai 400012, India*
[b] *Department of Radiation Oncology, Tata Memorial Centre, Mumbai 400012, India*
* Corresponding author.

Introduction. 3D conformal brachytherapy utilized limited source positions in catheters and thus may impact dosimetry for inter observer variation in target delineation.

Purpose. To investigate the inter observer variations in lumpectomy cavity (LC) and clinical target volume (CTV) delineation and their dosimetric impact.

Material and methods. Delineation of LC and CTV was done by five radiation oncologists on 20 patients of interstitial breast implant. Cavity visualization index (CVI), four point scale ranging from (0-excellent) to (3-poor) was developed for open cavity technique and assigned for each patient. Total 200 contours for all five observers and 100 geometrical optimized plans were made.

Spatial concordance (CI), average shift in the center of mass (COM) and SD of structure volume were quantified among all observers and statistically analyzed. Variation in source dwell positions for each tube and volume encompassing prescription isodose (Vmax/Vmin) among observers was estimated.

Results. The mean ± SD CI of LC and CTV was 0.54 ± 0.08 and 0.58 ± 0.08. Mean assigned CVI was 0.85 ± 0.81. CI tends to decrease and shift in COM increase significantly ($p < 0.05$) as CVI increased. Out of total 309(15.7 ± 3.3) implanted catheters, 20% catheters had no change, 37% and 20% catheters having variations more than 3 and 5 dwell positions (5 mm step size) respectively. The mean Vmax/Vmin of prescription isodose was 1.18 (range 1.03–1.56).

Conclusion. Significant correlation of CVI was observed with CI and COM shift. Inter observer variations have shown the impact on the source positions along catheters and thus have dosimetric impact on irradiation of breast tissue with prescription isodose.

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IMPLEMENTATION IN CLINICAL USE OF A NEW PLAN VERIFICATION SOFTWARE FOR CONFORMATIONAL AND MODULATED TREATMENTS

A. Barateau, J. Mesgouez, D. Autret, M. Bremaud, C. Di Bartolo, S. Dufreneix *, C. Legrand

Department of Medical Physics, Integrated Center for Oncology, Angers, France
* Corresponding author.

Introduction. Single point monitor units check is mandatory for all treatment plans in France. However, this check is not reliable for intensity modulated plans because of high dose gradients. A recently released solution called Mobius3D allows performing multiple treatment plan verifications.

Purpose. To evaluate this new software for 3D-conformational and intensity modulation treatment plans and to study the different metrics available for treatment plan verification.

Materials and methods. Single point dose calculations of 144 static fields selected by experimental design were compared to the TPS calculation (AAA, Eclipse, Varian). For intensity modulation plans, a DLG correction was determined by measurements in a cylindrical homogeneous phantom. Finally, several metrics were compared for 30 VMAT treatment plans.

Results. The mean difference between TPS and Mobius3D calculations for static fields is −0.2 ± 0.8% with a maximum of −2.5% in homogeneous medium but differences up to 5.7% were observed in the thoracic phantom. With a DLG correction set to −1.5 mm, the VMAT treatment plans had a mean gamma analysis inside the body of 96.2% but some went down to 66.4% due to regions located outside the fields. Results of the gamma analysis inside the PTV or the mean dose delivered to the PTV were more homogeneous.

Conclusion. A large tolerance level was applied in presence of heterogeneities for 3D-conformational. For intensity modulation treatment plans, the gamma analysis inside the PTV was considered reliable knowing that Mobius3D also provides gamma analysis for organs at risk.

Disclosure. No disclosure.

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DEVELOPMENT OF EXTERNAL DOSIMETRY AUDITS FOR ADVANCED TECHNOLOGY IN RADIOTHERAPY DOSE DELIVERY: AN IAEA COORDINATED RESEARCH PROJECT

J. Izewska [a], P. Wesolowska [a], W. Lechner [b], D. Georg [b], M. Tomsej [c,e,*], D. Followill [d], S. Kry [d], M. Tenhunen [e], J. Povall [f], D. Thwaites [g]

[a] *International Atomic Energy Agency, Division of Human Health, Vienna, Austria*
[b] *AKH, Vienna, Austria*
[c] *CHU Charleroi A. Vésale, Charleroi, Belgium*
[d] *IROC Houstonn QA Center, U.T. MD Anderson Cancer Center, Houston, USA*
[e] *University Hospital Helsinki, Finland*
[f] *St James' Institute of Oncology, University of Leeds, Leeds, UK*
[g] *University of Sydney, Australia*
* Corresponding author.

Introduction and purpose. An IAEA co-ordinated research project (CRP) is under implementation that develops methodology for remote dosimetry audits of IMRT techniques to be offered to radiotherapy centres by national audit networks in low and middle income countries.

Materials and methods. The CRP involves four audit steps: (i) remote verification of TPS calculation of small beam output factors relevant to IMRT (ii) dosimetry audit of MLC positional performance for IMRT using radiochromic film, (iii) film audit of single clinical IMRT field dose delivery and (iv) 'end-to-end' dosimetry audit for multiple field IMRT techniques using TLDs and radiochromic films. New procedures, phantoms, instructions and data sheets for audited centres were developed at the IAEA and tested through multinational pilot studies. Research groups from 14 countries participate in the CRP.

Results. The results of the first CRP step show agreement within 1% of participants' TPS output factors and the reference data for field sizes $\geqslant 4 \times 4\ cm^2$ but dose overestimation by TPSs by 2–3% for field sizes $\leqslant 3 \times 3\ cm^2$. The second step confirmed that most audited MLCs perform as expected. The results of the third CRP step show that TPS plans prepared by participants and delivered to films agree

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Interfraction variation in the target volume for accelerated partial breast irradiation (APBI) using intraoperative multicatheter interstitial brachytherapy and its dosimetric impact

Author(s): UPRETI, Ritu Raj[1]

Co-author(s): BUDRUKKAR, Ashwini [2] ; UPRETI, Udita [2] ; WADASADAWALA, Tabassum [2] ; MISRA, Shagun [2] ; DESHAPNDE, Deepak D [2]

[1] *Department of Medical Physics, Tata Memorial Centre, Mumbai, India*

[2] *Department of Radiation Oncology, Tata Memorial Centre, Mumbai, India*

Corresponding Author(s): rituraaj123@yahoo.com

Introduction of the study: Multi-catheter interstitial brachytherapy (MIB) is the oldest technique with longest follow-up for Accelerated Partial Breast Irradiation. Intra operative multicatheter interstitial brachytherapy requires duration of implant in situ is generally 7-10 days which may lead to post operative changes such as seroma formation and regression. This may result in variation in the lumpectomy cavity (LC) and the planning target volume (PTV) during the course of treatment. The present work aimed to investigate the dosimetric impact of interfraction variation in the target volume during accelerated partial breast irradiation for intra-operative breast implants.

Methodology: Intraoperative placement of flexible catheters was performed on sixteen patients who underwent computed tomography (CT1) based brachytherapy planning. The lumpectomy cavity was delineated on CT1 which included seroma, radio-opaque clips, and air in the cavity. Clinical target volume (CTV) was obtained by growing a uniform margin of 1 cm around the cavity. CTV was edited by limiting the skin by 0.5 cm and up to the chest wall. For brachytherapy CTV was considered as planning target volume (PTV). Catheter reconstruction was done on CT1 and active dwell positions of each catheter were obtained by giving a margin of 0.5 cm over CTV. Graphical optimization was done to yield optimum plan PCT1 for the treatment. CT was repeated prior to the last treatment fraction (CT2). Contouring of LC, CTV and catheter reconstruction were carried out on CT2. PCT1 was manually reproduced in CT2 which yielded plan PCT2. Plans were compared using coverage index (CI), dose homogeneity index (DHI), external volume index (EI), overdose volume index (OI) and conformal index (COIN). CI is the fraction of the LC or CTV receiving a dose equal to or greater than the prescription dose. EI is the ratio of the normal tissue volume outside the CTV receiving a dose equal to or greater than the prescription dose to the CTV. DHI is the fraction of breast tissues receiving a dose between 100% and 150% of the reference dose. OI is the fraction of the CTV receiving a dose equal to or greater than two times the reference dose. The COIN takes into consideration the coverage of the CTV by the prescription dose and also the unwanted irradiation of normal tissue outside the CTV. The data was compared and statistically analyzed by T-test for paired samples using Statistical Package for Social Sciences (SPSS version 20.0, IBM, Chicago) software.

Results: The mean volume of LC and PTV was 68.02 ± 27.95 cm3 and 138.84 ± 46.93 cm3 for PCT1 while it was 74.88 ± 31.33 cm3 and 146.56 ± 55.88 cm3 for PCT2. Mean CI of LC and PTV decreased significantly by 3.74% (r=0.024) and 8.64% (r=0.001) in PCT2. 11.8% and 10% increase in the mean EI and OI was observed in PCT2. Variation in the mean DHI was small and insignificant for both plans. Significant decrease (p=0.001) in mean COIN value was observed in plan PCT2 (0.538) compared to PCT1 (0.602).

Conclusion: The interfraction variation in the LC and CTV volume was found patient specific. Interfraction variation in the CTV volume has shown the significant impact on coverage and conformity of the target volume.