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Original Article

Adjuvant Irradiation in Carcinoma Breast Patients: Comparison of 3DCRT and Semi–automated Complex VMAT Hypofractionated Plans


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Abstract

Objective: Adjuvant radiotherapy is required for most post MRM breast cancer patients. Aim of treatment is to target radiation to region of interest while sparing Organs at Risk (OARs). Attempts are being made to decrease dose to OARs without compromising target coverage by evolving radiation techniques. In this study, a comparison of traditional 3DCRT plans is done with semi–automated complex VMAT plans for dose received by OARs namely Contralateral Breast (CLB), Ipsilateral lung (I/LL), and Contralateral Lung (C/LL).

Materials and Methodist was planned for 30 post MRM breast cancer patients for chest wall, ipsilateral axilla and supraclavicular lymph node. The PTV dose was 42.5 Gy in 16 fractions, 2.66 Gy/fraction, 5 days a week. For each patient traditional 3DCRT and semi–automated complex VMAT plans (conventional + tangential VMAT plans) were prepared and evaluated by radiation oncologists.

Results: Dose evaluation of CLB shows higher Dmax for 3DCRT plans, while, Dmean was lower for the 3DCRT plan. Difference between D2 was not significant. V2.5 was significantly less in 3DCRT, while, difference between V5 and V10 were not significant. For C/LL Dmean, V2.5, V5, and V10 were higher for the VMAT plan. For I/LL Dmean, V5 and V10 were higher, while V20 and V30 were lower for VMAT plans.

Discussion and Conclusion: The VMAT technique described here is a useful treatment option available for difficult planning situations. OARs stated above had a mixed result showing VMAT plans to be inferior at lower dose metrics, while, superior at higher dose metrics.

Keywords: 3DCRT, Semi–automated complex VMAT, Hypofractionated, Contralateral breast, Contralateral Lung, Ipsilateral Lung

Introduction

Adjuvant radiotherapy to the chest wall and the suspected nodal regions (supraclavicular, axilla, internal mammary) is an essential part of treatment for most of the post MRM breast cancer patients and it increases the local control rates and overall survival in these patients. Considerable interest should be paid towards a better Quality of Life (QOL) of these breast cancer survivors. While targeting the radiations to our region of interest, some of the radiations are also received by organs in the vicinity like lungs, contralateral breast, heart, brachial plexus, thyroid, etc. The radiation doses to these normal tissues may result in some late toxic effects which may adversely affect the QOL of patients. These Organs at risk (OARs) are being studied for a long time in terms of the dose received and the resulting complications. Attempts are being made to decrease the dose to these OARs by the evolving radiation planning and delivery techniques.

The traditional standard way of treatment planning has been the combination of two opposed tangential fields by 3–Dimensional Conformal Radiotherapy (3DCRT) technique, sometimes with the addition of subfields (field in field technique) at the same gantry angles, with anterior–posterior 3DCRT beams to the axilla and supraclavicular nodes (with junction matching), and sometimes electrons to the IM nodes. Some studies have suggested that inversely optimized Volumetric Modulated Arc Therapy (VMAT) technique, may improve coverage to the target tissue while

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Each patient was planned for adjuvant radiotherapy to the chest wall and regional nodes. These OARs receive low doses to a volume much greater than that would be delivered from the traditional 3DCRT breast treatment plans. These low-doses received by healthy organs may be associated with increased risk of secondary malignancies and other adverse events.

Contrary to conventional VMAT, a tangential VMAT (tVMAT) technique has been proposed to reduce the volume of the patient receiving low dose while at the same time maintaining good target coverage. However, this tVMAT does not allow for treatments of adjacent regional nodes, which require the use of conventional VMAT due to their complex shapes and proximity to OARs. Thus, for complex breast cases that require regional nodal irradiation, a combination of tangential VMAT arcs for the treatment of breast/chest wall, with a separate conventional VMAT arc limited to the axilla and supraclavicular nodes and any junction region is proposed. This method of combination VMAT provides great benefits by reducing the low dose region when irradiating the chest using tangential arcs in VMAT and maximizing coverage and OAR avoidance while irradiating axilla and supraclavicular region by conventional VMAT and improving dose homogeneity at the field junctions. This combination method is expected to achieve comparable low-dose spill to 3DCRT methods and would diminish the concerns about the significant low-dose spill from VMAT relative to 3DCRT in breast cases.

In the present study, a comparison of the conventional 3DCRT plans is done with the semi-automated complex VMAT plans for breast and chest wall cases with adjacent nodal volumes. From either plan prepared for each patient, a better plan is determined by comparing plan statistics and plan evaluation by the Radiation Oncology team.

Materials and Methods

Patient Selection: The present study is a single institutional dosimetric study, comprising of 30 breast cancer patients who have undergone Modified Radical Mastectomy (MRM) and are now being planned for adjuvant radiotherapy to the chest wall and regional nodes.

Simulation and Contouring: Each patient was positioned supine on the 16-slices CT-Simulator (Optima 580, GE Healthcare, Waukesha, USA) using a Breast Board LX (Macro Medic®s, Netherlands). Non–contrast Computed Tomography (NCCT) axial scans of 3.75 mm slice thickness were acquired from maxilla to mid liver while the patient was breathing freely. The contours were done in the Monaco Sim (V5.11.02 CMS Elekta, Sunnyvale, CA) contouring workstation. Contouring of chest wall and regional nodes were done using RTOG guidelines. Contouring of all relevant OARs including CLB, I/LL, and C/LL were done. The contours were then pushed to the Monaco workstation for treatment planning.

Treatment Planning: All patients were planned using Monaco® (V5.11.02) (Elekta CMS, Sunnyvale, CA) treatment planning system (TPS). A PTV dose of 42.5 Gy in 16 fractions, 2.66 Gy per fraction, delivered 5 days a week was planned for chest wall including ipsilateral axilla and supraclavicular lymph node regions. For each patient, the treatment plans were prepared using conventional 3DCRT and combined VMAT techniques and the dose distribution was optimized and normalized as per International Commission on Radiation Units and Measurements (ICRU) reference point of the breast. For dose constraints, QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) recommendations were followed.

3DCRT Planning: The 3D Conformal Radiotherapy (3DCRT) planning consisted of conventional medial and lateral tangential wedge portals with MLC field–shaping conforming to the target volume, for the supraclavicular and axillary PTVs, AP beam was used. Mono–iso–centric plans were created by placing the iso–center point at the end of the superior edge of the chest wall, both the tangential and supraclavicular fields were then set by this isocenter and calculated using Collapsed Cone (CC) dose calculation algorithm. Relative beam weights, wedge angles, and sub–fields were titrated until the desired dose distribution was obtained. Beam placement and PTV coverage of a 3DCRT plan are shown in Figure 1–A.

VMAT Planning: All Tangential Volumetric Modulated Arc Therapy (VMAT) plans were created by dual tangential arcs with a 6MV photon beam to get clinically acceptable dose distribution of PTV. The arc lengths of the VMAT plan varied from 30° to 40° depending upon the PTV size and each tangential beam incorporated three arcs. For the supraclavicular and axillary PTVs, dual iso–centric VMAT plans were created with the same tangential arc method as described above and an anterior arc of the same arc length was used with different iso–center located at the level of supraclavicular and axillary nodes. In all plans, a 2.5 cm skin flesh margin was used in the optimization to incorporate the PTV motion due to free–breathing. All the plans were optimized using the Monte Carlo (MC v1.6) dose calculation algorithm with a maximum number of control points 75 per arc, grid size of 0.3 cm, minimum segment width of 1 cm, medium level fluence smoothing and a calculation uncertainty of 2%. Beam placement and PTV coverage of a VMAT plan are shown in Figure 1–B.
Plan Evaluation: Both kinds of plans were evaluated for each patient and the dosimetric data were derived from the Dose Volume Histograms (DVH) for CLB, C/LL, and I/LL in terms of Dmean (volume-weighted mean dose, in Gy); D2 (the minimum dose received by the most irradiated 2% of the structure volume, in Gy); V2.5 (relative volume exposed to 2.5 Gy dose, in %), similarly V5, V10, V20, etc. were also calculated. The acceptable PTV coverage was set to be 95% of PTV volume receiving at least 95% of the prescribed dose. These data were collected from the plans that were approved, each in both categories (3D CRT and VMAT).

Results

The comparison of dose-volume factors of both plans in terms of CLB, I/LL, and C/LL are summarized in Table 1. The statistical significance was determined using paired t-test, and with the null hypothesis (H0) that there was no difference between the two planning techniques, and the statistical significance set at \( \alpha = 0.05 \).

On comparing the 3DCRT and VMAT plans with acceptable coverage it was found that the dose to OARs stated above had a mixed result with VMAT being superior at higher dose metrics, while 3D CRT being superior at lower dose metrics. This may be explained by the low dose spillage of the radiation in the nearby structures in VMAT plans. The representative image of 3DCRT and VMAT plans is shown in Figure 2 explaining the low dose spillage of radiation in the VMAT plan.

Contralateral breast: Dose evaluation of CLB in our study shows a significant difference between the maximum doses (Dmax) in favor of the VMAT plan, while, mean dose of CLB (Dmean) was significantly lower for 3DCRT plan. The difference between the minimum doses received by the most irradiated 2% of the structure volume (D2) was not significant. The volume receiving 2.5 Gy (V2.5) was significantly less in 3DCRT as compared to VMAT, while the difference between V5 and V10 was not significant statistically.

Contralateral Lung: For the Contralateral lung, the mean dose (Dmean) received was higher with the VMAT plan. Similarly, V2.5, V5, and V10 were higher for the VMAT plan. The difference between all these above-stated parameters was statistically significant.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3DCRT</th>
<th>VMAT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmean (cGy)</td>
<td>59.69±23.59</td>
<td>250.00±86.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V2.5 (%)</td>
<td>0.24±0.54</td>
<td>0.69±1.23</td>
<td>0.042</td>
</tr>
<tr>
<td>V5 (%)</td>
<td>40.05±4.31</td>
<td>49.30±8.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V10 (%)</td>
<td>33.14±4.27</td>
<td>29.07±2.67</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1: Dose Statistics Comparison of 3DCRT vs. VMAT for CLB, C/L Lung, and I/L Lung. The Displayed Values are the Mean, Standard deviation, and P-value Using Paired t-Test.

- 3D CRT – Three-Dimensional Conformal Radiotherapy
- VMAT – Volumetric Modulated Arc Therapy
- CLB – Contralateral Breast
- C/L Lung – Contralateral Lung
- I/L – Ipsilateral Lung
- Dmean – Maximum Dose, Dmax – Mean Dose
- Vx is the volume receiving x% of the prescribed dose.
- Dx% is dose received by x% of volume.

Figure 1: (A) – 3DCRT plan, PTV coverage, and beam placement; (B) – VMAT plan, PTV coverage, and beam placement.
Discussion and Conclusion

Adjuvant radiation treatment in post–MRM breast cancer patients is required in most of the cases. The advent of multimodality treatment and personalized medicine in the past few years has improved patient survival from this widespread disease. With an improvement in survival, avoidance of toxicities has become even more important. For achieving optimal irradiation results for these patients with breast cancer, the best local control, lowest acute toxicities, and late toxicities and lowest second malignancy induction, advanced irradiation techniques are used. In the case of breast irradiation, sparing of OARs is of substantial importance in order to avoid late toxicities in breast cancer patients who are likely would have longer survival rates. Several conformal techniques have evolved from 3DCRT to IMRT and VMAT in order to maintain the coverage of target and minimize the dose to OARs. Further doses to OARs like heart and lungs are reduced when these techniques are combined with breath–hold techniques. In the absence of breath–hold techniques, wider PTV margins are used to compensate for breathing movements.

Ipsilateral Lung: The mean dose (Dmean), V5, and V10 were higher, on the contrary V20 and V30 were lower for VMAT plans as compared to 3DCRT plans. The difference between all these above–stated parameters was statistically significant.

In Figure 3, the representative dose–volume histogram (DVH) of PTV coverage and doses to above OARS is shown.

Figure 2: (A, B) Shows axial and coronal sections of dose spillage in 3DCRT plans, (C, D) Shows axial and coronal sections of dose spillage in VMAT plans.

Figure 3: (A) Shows dose volume histogram (DVH) for PTV, Contralateral Breast (CLB), Contralateral lung (C/L Lung), and Ipsilateral lung (I/L Lung) comparing 3DCRT and VMAT plans.
In the present study, the 3DCRT and complex VMAT plans (conventional + tangential) were compared for post MRM breast cancer patients in whom adjuvant radiation was indicated to the chest wall and regional LN (supraclavicular and axillary nodes). In this study, hypofractionated plans were compared in both categories. Hypofractionated postmastectomy radiotherapy has now been implemented in many institutes for breast irradiation. Since the institutes serving large numbers of cancer patients have a long waiting list, a lower total dose in a smaller number of fractions could offer similar clinical outcomes with decreased machine load. The updated results of a Canadian landmark trial has shown that hypofractionated regimen using 42.5 Gy in 16 fractions following breast—conserving surgery for treating early stage breast cancer shows locoregional control, overall survival, and cosmetic outcomes similar to the standard conventional radiotherapy at 10–years follow–up. Another two large randomized controlled trials, START A and START B trials from the UK, have also confirmed that the hypofractionated regimens (41.6 Gy in 13 fractions, 39 Gy in 13 fractions, and 40 Gy in 15 fractions) are safe. These trials concluded that rates of tumor control and the normal tissue damage were similar to that of conventional fractionation schedule of 50 Gy in 25 fractions. There are many other studies comparing hypofractionated RT and conventional RT but literature does not provide much data on comparing hypofractionated 3DCRT plans with hypofractionated VMAT plans with respect to OAR doses. The present study compares 3DCRT and VMAT plans for hypofractionated dose regimens for breast irradiation and the results obtained in our study are discussed below.

PTV Coverage

Various plans were prepared for each of the patient with 3DCRT and VMAT techniques, each of the plans was evaluated by the team of radiation oncologists. A plan with adequate PTV coverage (95% dose to 95% of PTV volume) and acceptable OAR doses was accepted from each category for comparison. This study was limited to doses to OARs namely contralateral breast, ipsilateral lung, and contralateral lung, so a detailed analysis for PTV parameters was not conducted.

Dose to Contralateral Breast

As the treated patients of breast cancer have longer survival, there is a risk of developing secondary malignancy in the contralateral breast over the lapse of time. This risk of secondary malignancy is due to the small doses of scattered radiation received by the CLB. Sometimes medial portion of CLB also receives high doses of radiation from medial tangential fields directly, more in the case of 3DCRT plans. For VMAT plans a dose constraint of $V_{5\text{Gy}} < 15\%$ was selected as an optimization parameter and care was taken to avoid compromising PTV coverage.

In our study, the maximum dose (Dmax) received by the CLB in the 3DCRT plan was almost twice that received in VMAT plans. The Dmax in 3DCRT and VMAT plans were $2646.84 \pm 1297.01$ cGy and $1258.52 \pm 722.61$ cGy respectively. This can be explained by the close proximity of the medial region of CLB to the medial tangential field placed for chest wall irradiation in 3DCRT plans.

The mean dose (Dmean) received by CLB was higher for VMAT plans as compared to 3DCRT plans. The Dmean for 3DCRT plan was $103.22 \pm 31.88$ cGy and for VMAT plan it was $174.09 \pm 42.11$ cGy. The difference between the two values was statistically significant (p-value < 0.001). In the study conducted by Sudha SP et al, the mean doses were $1.77 \pm 1.46$ Gy and $5.83 \pm 1.71$ Gy for the 3DCRT and VMAT plans respectively. The difference between the numerical values of Dmean of 3DCRT and VMAT plans in our study is not huge enough but only approximately 6 to 9 cGy, this difference though little is in favor of 3DCRT for all patients which are signified by the p-value. Though such a mere difference should not have any clinically significant adverse outcome.

$V_{2.5\text{Gy}}$ was more for VMAT plans ($11.99 \pm 6.28$ cGy) as compared to 3DCRT plans ($7.62 \pm 3.32$ cGy), p-value 0.002. The difference between $V_{5}$, $V_{10}$ and $D_{2\%}$ was not significant between the two plans.

Both the techniques place the CLB in the high–risk group for secondary malignancy as it might receive more than 1 Gy. The mean dose was expected to owe to the exit dose of the arc deposited over a larger area of the CLB.

Dose to Contralateral Lung

An optimization value of $V_{5\text{Gy}} < 15\%$ was selected for VMAT plans. However, care was taken not to compromise the PTV coverage which may deleteriously impact the disease–free survival of patients.

The Dmean for VMAT and 3DCRT plans were $250.00 \pm 86.32$ cGy and $59.69 \pm 23.59$ cGy respectively. The Dmean for VMAT plan was significantly higher as compared to 3DCRT plans though the mean dose received was much lower than the lung tolerance dose.

The values of $V_{2.5\text{Gy}}$, $V_{5}$, and $V_{10}$ were also higher for VMAT plans as compared to 3DCRT plans. All the differences were statistically significant in favor of 3DCRT.

The contralateral lung doses are not compared for 3DCRT and VMAT plans in the literature available. The clinical significance of the minor doses received by
contralateral lung is also not known. The only concern that can be raised for the doses received is the possibility of secondary malignancy relating to the stochastic effect of radiation. The low dose spill of the VMAT plans results to the delivery of a comparatively higher dose to contralateral lung.

**Dose to Ipsilateral Lung**

We selected $V_{30} < 30\%$ and $V_{30} < 15\%$ as the optimization parameter in this study. In case the optimizing constraints for V30 were not achievable in view to maintain PTV coverage, a higher V30 dose was accepted keeping the mean dose <17 Gy.

In the VMAT plan, a significant reduction in the $V_{30}$ and $V_{20}$ values were found in the ipsilateral lung when compared to the 3DCRT plan. V20 and V30 for VMAT plans were 29.07 ± 2.67 % and 19.23 ± 2.72 % while for 3DCRT plans they were 33.14 ± 4.27 % and 27.24 ± 4.40 % respectively. The low dose volumes i.e. $V_2$ and $V_{10}$ were significantly higher for VMAT plans compared to 3DCRT plans.

The Dmean for VMAT plan was 1557.22 ± 146.94 cGy and for the 3DCRT plan it was 1477.81 ± 147.47 cGy. The difference between the two values was significant statistically with a p-value 0.018.

A similar pattern was found in the study conducted by Sudha SP et al., the V20 Gy (34.94 vs. 24.42) and V30 Gy (32.32 vs. 16.19), for the ipsilateral lung were significantly higher for the 3DCRT plans when compared to VMAT plans ($P = 0.000$). Their study also revealed the superiority of VMAT plans over 3DCRT plans at higher dose metrics.

The above discussion shows that tVMAT offers various advantages over 3DCRT particularly in the high dose range. Although the low-dose spill and the mean doses are higher in tVMAT, it is yet to be conclusively proven whether such meager differences produce clinically significant adverse effects. Importantly, the excess relative risk for radiation-induced carcinogenesis by acute irradiation is 0.86 per Gy which can be decreased by 2 to 10 times when the same is fractionated (Safora Johansen et al, ActaOncologica). This further emphasizes that this particular area is a grey zone and needs further validation. The increased low dose spill, though a bothersome aspect, needs further validation and is significantly outweighed by the survival advantage offered by radiotherapy.

A study done by Byrne et al. comparing 3DCRT with tVMAT in breast radiotherapy demonstrated significantly higher beam-on time and monitor units with tVMAT which is another factor that might impede the routine use of tVMAT in treatment of carcinoma breast, especially in high volume centers where the total patients treated is heavily dependent on the individual patient treatment time. The increased treatment times also give way to theoretical concerns of loss of tumor control from the radiobiological perspective.

This study shows that tVMAT is a feasible modality in the radiation treatment of carcinoma breast and is especially advantageous in the high dose ranges, useful to reduce the maximum doses received by the important OARs. Though routine use of tVMAT needs robust infrastructure, it is clear that tVMAT is advantageous when the conventional 3DCRT plans are unable to achieve the constraints.

**References**


