# TABLE OF CONTENTS

## Original Studies

**Mutations in EGFR Signal Pathway in Correlation with Response to Treatment of Head and Neck Cancers** ........................................ 07  

**Comparison of IMRT and Rapidarc treatment plans using AAPM task group test suites** ................................................................. 11  
S. Sathiyan, M. Ravikumar, A.L. Boyer, J. Shoales  

**Clinical significance of hTERC and C-Myc genes amplification in a group of Egyptian patients with cancer cervix** ............. 18  
M.M. Eid, H.M. Nossair, M.T. Ismael, G. Amira, M.M. Hosney, R. Abdul Rahman  

**Disease profile and treatment results of anal canal SCC: Experience from AIIMS, New Delhi** ............................................................. 27  
R. Hadi, BK Mohanti, S. Palhy, NK Shukla, SVS Deo, A. Sharma, V. Raina, GK Rath  

**Prediction of Anthracycline Induced Cardiotoxicity: Study of thirty-one Iraqi adult patients** ...................................................... 33  
AMJ Al-Mudhafar, AAS Ali  

**Early Gastrointestinal Complications of Stem Cell Transplant - Results of Prospective Study at IRCH, AIIMS, India** ............ 40  
G.M. Bhat  

**Medullary Carcinoma of the Breast: Ten Year Clinical Experience of the Kuwait Cancer Control Centre** ......................... 45  
S.M. Samir, M.S. Fayaz, A. Elbasmy, M.M. Motawy, S. Abuzallouf, T. George, M. Abdelhady, A. Bedair  

**Respiratory gated simultaneous integrated boost-intensity modulated radiotherapy (SIB-IMRT) after breast conservative surgery for carcinoma of the breast: The Salmaniya Medical complex experience** ............................................. 53  
D. Majumdar, S.S. Mohammed, M.A. Naseer, J. Jacob, R. Mohan, S.B. Ebenezer, B. Al-Najjar, S. Al-Janahi, V. Ramanathan, S.A. Sabt, R.S. Patnaik, A. Hassan  

## Case Reports

**Temporary Asymptomatic Sinus Bradycardia with Carboplatin, Paclitaxel and Bevacizumab: Under-reported in Clinical Trials and under-disclosed in practice** .............................................................. 60  
J. Zekri  

**Verruciform xanthoma of the penis in a young male masquerading as squamous cell carcinoma: Case Report** ..................... 65  
M. Kukreja, M. Kamal, R. Ray, AASR Mannan  

**Acute respiratory distress syndrome in poor prognostic germ cell tumor with multiple lung metastases: A case report** .......... 69  

## Conference Highlights /Scientific Contribution

- Highlights of the 5th GFFCC Conference on Colorectal Cancer, Sharjah, UAE .......................................................... 72  
- Abstracts of the 5th GFFCC Conference on Colorectal Cancer, Sharjah, UAE .......................................................... 75  
- News Notes ........................................................................................................................................................................ 87  
- Scientific Activities in the GCC and the Arab World (2nd half of 2011) ........................................................................ 88
Respiratory Gated Simultaneous Integrated Boost-Intensity Modulated Radiotherapy (SIB-IMRT) After Breast Conservative Surgery For Carcinoma Of The Breast: The Salmaniya Medical Complex Experience

D. Majumdar, S.S. Mohammed, M.A. Naseer, J. Jacob, R. Mohan, S.B. Ebenezer, B. Al-Najar, S. Al-Janahi, V. Ramanathan, S.A. Sabt, R.S. Patnaik, A. Hassan

Department of Radiation Oncology, Salmaniya Medical Complex, Kingdom of Bahrain

Abstract

Purpose
To present our clinical experience using SIB-IMRT Technique for Intact Breast cancer.

Materials and Methods
A retrospective review of 45 cases of Stage I-IV breast cancer patients treated with SIB-IMRT with respiratory gating after conservative treatments from 25th November 2008 to 16th February 2010. The most common fractionation was 1.8 Gy to Ipsilateral Breast tissue and 2.2 Gy to the lumpectomy cavity giving whole breast dose as 50.4 Gy and Lumpectomy cavity dose as 61.6 Gy over 28 fractions concomitantly. Respiratory gating was done and CT-images were taken in inspiratory breath hold position.

Results
A total of 45 patients with breast cancer - stage I (17.7%), II (71%), III (8.9%), IV (2.2%) were treated with SIB-IMRT with respiratory gated radiotherapy. Out of 45 patients, 24 are of left sided breast cancer and 21 are of right sided breast cancer patients. The median, Dose maximum (D-max) in SIB-IMRT is 106.2% of prescribed lumpectomy site dose. The median isodose line prescribed to PTV-2 is 100%. The Conformity index (CI) is 0.9688 (median value) and Homogeneity index (HI) 1.06 (median). The median ipsilateral lung, mean dose is 21.66 Gy and V-20 is 37.4%. For left sided cases the median value of mean heart dose, V-30 and V-40 are 22.98 Gy, 23.45% and 9.45 % respectively. Acute skin toxicity was of Grade-I in 2.2 %, Grade-II in 64.4 %, Grade-III in 31.1 %, and Grade-IV in 2.2 %. The global Breast cosmoses were seen excellent in majority (93%) of case at median follow up of 8 months duration.

Conclusions
Breast SIB–IMRT Technique is feasible and comparable with other treatment techniques with reduced treatment duration by six fractions. At median follow up of 8 months the skin toxicity and cosmoses are excellent in high percentage of cases.

Keywords
Breast Cancer, Intensity Modulated Radiotherapy, Simultaneous Boost
Gy - 2 Gy per fraction) is the standard approach for patient treated with breast conservative surgery, although recent studies have shown that hypofractionation schedule may yield similar outcome in selected patients. An additional boost dose of 10-16 Gy to the lumpectomy cavity reduces Ipsilateral Breast Tumor Recurrence (IBTR) with a relative risk reduction of nearly 50% in all patients; however absolute benefit is greatest in women aged < 50 years and in older women with high grade tumors and/or lymph vascular invasion. Still, lesser number of indicated patients receive radiotherapy because referring physicians are scared of radiotherapy side effects. For the last half-century, breast irradiation is done by two parallel opposing tangential beams. Moreover, more women are subjected to potential complications of RT, namely (a) radiation to heart (b) radiation to lung (c) contra lateral breast (d) Chest wall fibrosis and (e) poor cosmeses due to dose inhomogeties. Compared to conventional tangential breast radiotherapy, IMRT is a treatment approach that reduces acute skin toxicity and also reduces the risk of normal tissue complication. This article presents the early experience at our institute on respiratory gated SIB-IMRT, with study on dosimetry, acute toxicity, cosmesis and normal tissue dose.

Materials and Methods

Patients with carcinoma of breast treated with conservative surgery (BCS) and with SIB-IMRT were evaluated. Total number of breast cancer treated with SIB-IMRT following BCS were 45 over 2 years. All patients underwent staging work-up and were staged according to 6th edition of AJCC manual. Patients underwent wide local excision with axillary clearance according to practice guideline, surgeon preference and patient’s wishes. According to available evidences, patients received systemic chemotherapy, hormonal therapy and Trastuzumab. Neo-adjuvant chemotherapy was employed for locally advanced breast cancer. Radiotherapy was started 3 weeks after completion of surgery and chemotherapy. Patient was simulated in wide bore Phillips CT simulator. Patients were immobilized by whole body vac lock. Patient positioned in supine with arm above the head and head was kept in neutral position. IV Contrast was not given routinely. Respiratory gating was done and images were taken in breath hold position. Slice thickness was 5 mm, all axial cuts images were taken in 0 degree Gantry angle. From mandible to upper abdomen, all were scanned. DICOM Images were transferred to Eclipse planning system.

Target Definition:

Meticulously, the tissue at risk and the normal structures were delineated according to clinical and radiological data in the CT-Images taken on breath hold. Towards the later part the RTOG-Breast cancer atlas is used as the guideline for target delineation. CTV-1 is the whole breast and SCF+ Axilla level I, II, III as per indication. PTV-1 is the three dimensional margin of 5mm around CTV-1 except anteriorly towards the skin is zero (skin flash tool is used) and posteriorly towards the lung is 7 mm or as per gating values. The PTV-2 is created with an outer margin of 5mm -1cm from CTV-2 which is lumpectomy cavity, guided by surgical clips. The normal structures were contoured as Ipsilateral Lung, Bilateral Lung, Spinal cord, Heart, Esophagus, Opposite Breast and Liver.

Dose Definition:

Dose to PTV-1 prescribed is 50.4 Gy in 28 fractions at 180 cGy per fraction and to PTV-2 is 61.6 Gy in 28 fractions to 64.4Gy in 28 fractions at the dose 220 cGy - 230 cGy per fraction. Normal tissue dose constraint were given as Ipsilateral lung V20 <30 -35 %, Heart V30 ≤30%, V40 ≤ 20%, Mean dose ≤20%, Opposite Breast mean dose less than 5 Gy and spinal cord maximum point dose less than 40 Gy.

To compare SIB-IMRT fractionation with conventional sequential boost schedules, a biologically equivalent dose (BED) was calculated using the linear-quadratic (LQ) model:

$$\text{BED} = D \left[ 1 + \frac{d}{\alpha/\beta} - \frac{\gamma Tt}{\alpha} \right]$$

Where D = total dose, d = the dose per fraction,
\( \alpha, \beta = \text{LQ parameters} \),
\( Tt = \text{total treatment time in days} \),
\( \gamma = \ln(2)/Tpot \), where \( Tpot \) is the potential doubling time.
\( Tpot = 15 \text{ days} \)
\( \alpha = 0.3/ \text{Gy} \)
\( \alpha/\beta = 10 \text{ days (tumor)} \)
\( \alpha/\beta = 3 \text{ days (normal tissue)} \)

The SIB fractionations mainly used 28 fractions of 2.2 Gy to the boost volume are equal to BED of 25 fractions of 1.8 Gy to whole breast followed by 8 fractions sequential boost of 2 Gy per fraction in terms of tumor control and late effect.

**Treatment Planning:**

A 4 to 7 beam arrangements were done to cover PTV-1 and PTV-2. Skin flash of 1.5 cm beyond the breast tissue was done. Fields were optimized to maximize coverage and minimize heterogeneity. Dynamic IMRT technique using 6 MV photon was employed for all patients. The PTV-1, PTV-2 Volumes were intended to be covered by 95% of prescription dose and keeping less than 110% excluding PTV-2 volume as end points. The total dose was prescribed to PTV-2.

**Assessment of Toxicity:**

The toxicity was graded according to RTOG Toxicity criteria which were documented on weekly patient review notes. Skin toxicity was from Grade-0 through Grade-IV. Global Breast cosmesis were reviewed as poor, good and excellent. Cosmetic results were evaluated at each follow-up visit by the treating radiation oncologist or surgeon, using the Harvard criteria\(^\text{(16)}\) The arm edema was scored as nil, mild, moderate and severe. Patients were assessed at 3 month intervals after completion of radiotherapy. Arm circumference was measured when there was clinically evident swelling of the arm or if a patient complained of arm swelling. Measurements were obtained 10 cm above and below the bilateral antecubital fosse. Severe, moderate, and mild arm lymphedema were defined as a difference of greater than 3 cm, 2.1 to 3 cm, and 0.5 to 2 cm, respectively. in the circumference at one or more measurement sites between the treated and untreated sides.

\(^{17}\) Available patient data were reviewed retrospectively for documented Radiation Pneumonitis (RP) with the help of SWOG Toxicity criteria.\(^{18,19}\)

**SWOG Toxicity criteria:**

Grade- I (mild) chest x-ray, CT changes +, clinical Sm +, but do not require steroid; Grade-II (moderate) steroids are required; Grade- III (severe) when oxygen is needed; Grade-IV (life threatening) when assisted ventilation is required; Grade-V (death) treatment is fatal. Cardiac ejection fraction was evaluated as per ECHO cardiograph.

**Results**

**Patient and Tumor Characteristics:**

From 25 November 2008 to 16 February 2010, a total of 45 breast cancer patients was treated with SIB-IMRT. Median age of the patients was 49 years (29-60 yrs). Out of 45 patients, 24 (53.3%) were left-sided breast cancer and 21 (46.7%) were right-sided breast cancer patients. The stage distribution were as stage I (17.7%), stage II (71%), stage III (8.9%) and stage IV (2.2%). Tumor characteristics were as T1 (31%), T2 (62%) and T3 (7%).

**Dosimetric Characteristics:**

The numbers of treatment fields are 4-7 in number. The median number of fields is 5 in number. Median PTV-1 Volume is 1730.9 cc (986.6 – 4119.8 cc) and PTV-2 Volume is 285.2 cc (44.6-549 cc). The intentions of all plans are to deliver at least 95% of Prescribed Dose (PD) to 95% of PTV-1, PTV-2. The median, Dose maximum (D-max) in SIB-IMRT is 106.2% of prescribed lumpectomy site dose. The median isodose line prescribed to PTV-2 is 100%. The Conformity index (CI) is 0.9688 (median value) and Homogeneity index (HI) 1.06 (median). The median value of monitor unit is 1321 MU. The percentage of PTV-1 volume getting more than 110% was 5.3% (median) and the median value of mean PTV-1 dose is 52.86 Gy (104.9%). The volume of PTV-1 covered by 95% of PD is 93.7% (median). Similarly the percentage of PTV-2 volume getting more than 110% was 0% (median) and median value of mean PTV-2
dose is 61.6Gy (100%). The volume of PTV-2 is covered by 95% of Prescribed Dose is 93.9 % (median).

Normal Tissue Dose:

The median ipsilateral lung mean dose is 21.66 Gy, V-20 is 37.4% (median) and ipsilateral lung V-30 is 24.8 % (median). Out of 45 cases, 24 cases with left-sided breast cancer patients were evaluated for heart dose. The median value of mean heart dose, V-30 and V-40 are 22.98 Gy, 23.45% and 9.45 % respectively. Opposite breast mean dose was calculated. The median value of mean dose to opposite breast was 5.5Gy.

Outcomes:

The acute skin toxicity was Grade I 2.2%, Grade II 64.4%, Grade III 31.1% and Grade IV 2.2%. Out of all the patients, majority (93%) of cases had excellent cosmoses. Out of all the patients, 53% of cases had mild and 44.4% had moderate arm edema whereas none had severe edema. Most of the patients (93.35%) were free from any chest symptoms or dry irritating cough and only 6.7% of cases complained some sort of breathing difficulty and dry cough. Out of this, one patient was positive for H1N1 virus. On follow up, none of the patients complained of symptoms pertinent to heart disease.

Discussion

Very few studies have been done to evaluate the potential benefits of IMRT in the intact breast. In a study by R. Singla et al in left-breast SIB-IMRT plan the target coverage was by 95% of prescription dose without increasing the maximum dose. They also concluded that SIB-IMRT was able to reduce lung mean dose, maximum dose and V20. It also reduced the maximum heart dose by 1032-1173cGy. However, the mean heart dose was significantly increased by 189-227cGy[20]. In a study by Hong et al, tangential beam IMRT, compared with tangential wedged beams, showed reduction of dose to the coronary arteries, contralateral breast, ipsilateral lung, and surrounding soft tissues[21]. Pignol JP et al[9] published the report of their randomized multicentre trial of 358 patients of Breast IMRT to reduce acute radiation dermatitis and showed that breast IMRT significantly reduced the occurrence of moist desquamation compared with standard wedge technique. The cosmetic outcome following radiotherapy for intact breast is dependent on various factors. Dose in homogeneities related to breast irradiation has been associated with poorer cosmetic outcome[22]. The size of the breast also influences the cosmetic outcome[23]. Vicini et al in a study of 281 patients treated with static multileaf collimator IMRT showed not only improved homogeneity across the breast, but did show with minimal toxicity and excellent cosmoses[24]. Ellen D et al published a phase III study report of 240 patients and found statistically significant higher incidence of late adverse effects of radiation and changes in breast appearance in patients in standard 2D treatment arm compared with the IMRT arm[25]. Radiation induced pneumonitis following tangential irradiation occurs in less than 5% of patients treated with tangential fields[26]. Krengli M et al reported a prospective study of Lung High Resolution CT (HRCT) and Pulmonary Function Test (PFT) of 41 patients after BCT and Radiotherapy. The lung changes mainly related to damage of alveolar capillary barrier and smallest airway ramifications were seen at 3 months with only partial recovery at 9 months after RT. The radiologic changes correlated significantly with the Dose Volume (DV) Parameters, showing that pulmonary toxicity will be minimum by limiting volume receiving 25 Gy or more to less than 100 cc3[27]. Lind et al predicted that lung complication can be avoided if ipsilateral V20 is kept below 30 %[28]. Various dosimetric parameters have been assessed as predictors for the development of Radiation Induced Lung Injury (RILI). This has been facilitated by the routine use of computed tomography–based treatment planning. Three widely studied and commonly used parameters include the mean lung dose (MLD), the volume of lungs receiving a specified dose, and normal tissue complication probability (NTCP). Mean lung dose (MLD) of ≤15 Gy, 17.5 to 20 Gy, 22.5 to 25 Gy, and ≥27.5 Gy resulted in 0%, 13%, 21%, and 43% incidence of all grades of RILI[29]. In a pooled analysis of 540 patients who received thoracic radiation by Kwa et al, the MLD was found to correlate with an increased
risk of pneumonitis\(^{(18)}\). In a prospective study of 99 patients, the most important factors predicting for RILI were the percent volume of the total lung receiving a dose greater than 20 Gy (V20) (\(P = 0.0013\)), MLD (\(P = 0.016\)), and the location of tumor in the lower lobe (\(P = 0.02\))\(^{(30)}\). On multivariate analysis, however, only V20 was found to predict for RILI. Similarly, the volumes of lungs receiving a specified dose have also been reported to predict for pneumonitis, including V10, V20, V25, V30, and so on\(^{(31)}\). The adverse cardiac effects of RT in women treated for breast cancer are related to both the volume of heart irradiated and the radiation dose delivered to that volume. Data from mantle field irradiation indicates that cardiac dose less than 30 Gy produce few cardiac events\(^{(32)}\). A study of regional and global cardiac function of 114 left-sided breast cancer patients showed perfusion defects 6, 12, 18, and 24 months after RT was 27%, 29%, 38%, and 42%, respectively. This perfusion defects is volume dependent\(^{(33)}\). Data from randomized trials, tumor registry studies, and retrospective reviews have yielded conflicting results on the extent of cardio toxicity on the basis of different treatment techniques. In our study we approached to keep the mean dose and V-30 as less as possible without compromising the coverage. Breast irradiation has not been associated with an increase in contralateral breast cancers as compared to non-irradiated breast (surgical) controls in randomized clinical trials\(^{(34-37)}\). Patients with genetic predisposition to breast cancer, contralateral breast dose is quite significant and clinical judgment must be exercised\(^{(38)}\). Khan et al studied 1,755 patients of breast cancer treated with breast conservative surgery and radiation therapy. Fifty nine patients developed contralateral malignancy and found that there is no medial quadrant preponderance in location of tumor\(^{(39)}\). It is prudent to keep the dose to opposite breast as low as possible. Table I shows the comparative results of various relevant studies comparing with our SMC results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Tech</th>
<th>No. Cases</th>
<th>Breast Dose</th>
<th>Boost Dose</th>
<th>No.Fx</th>
<th>Mean Heart Dose</th>
<th>Ipsilateral Lung dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBCA (40)</td>
<td>2006</td>
<td>IMRT</td>
<td>5</td>
<td>50</td>
<td>None</td>
<td>25</td>
<td>12.8</td>
<td>15.1%</td>
<td>PS</td>
</tr>
<tr>
<td>UAB(41)</td>
<td>2007</td>
<td>IMRT</td>
<td>10</td>
<td>45</td>
<td>None</td>
<td>25</td>
<td>1.4-2.3</td>
<td>NR</td>
<td>PS</td>
</tr>
<tr>
<td>UPMC(42)</td>
<td>2007</td>
<td>IMRT</td>
<td>20</td>
<td>50</td>
<td>None</td>
<td>25</td>
<td>2.3</td>
<td>7.2%</td>
<td>PS</td>
</tr>
<tr>
<td>LOYOLA(20)</td>
<td>2006</td>
<td>SIB-IMRT</td>
<td>10</td>
<td>50.4</td>
<td>66.4</td>
<td>28</td>
<td>5.25</td>
<td>12.5%</td>
<td>PS</td>
</tr>
<tr>
<td>NYU(43)</td>
<td>2007</td>
<td>SIB-IMRT</td>
<td>91</td>
<td>40.5</td>
<td>48</td>
<td>15</td>
<td>2.0</td>
<td>1.3%</td>
<td>CS-Prone</td>
</tr>
<tr>
<td>NETHERLAND (44)</td>
<td>2007</td>
<td>SIB-3DCRT</td>
<td>30</td>
<td>50.7</td>
<td>64.4</td>
<td>28</td>
<td>4.8</td>
<td>5.5%</td>
<td>CS</td>
</tr>
<tr>
<td>EMORY (45)</td>
<td>2009</td>
<td>SIB-IMRT</td>
<td>360</td>
<td>45</td>
<td>59.92</td>
<td>28</td>
<td>2.6</td>
<td>10.6%</td>
<td>CS-165 Left</td>
</tr>
<tr>
<td>SMC</td>
<td>2010</td>
<td>SIB-IMRT</td>
<td>45</td>
<td>50.4</td>
<td>61.6</td>
<td>28</td>
<td>18.8</td>
<td>37.4%</td>
<td>CS</td>
</tr>
</tbody>
</table>

Table 1 : Comparative results of various relevant studies comparing with our SMC results.

Abbreviations: fx = fractions; IMNs = internal mammary lymph nodes; IMRT = intensity-modulated radiation therapy; NR = not reported; PS= planning system generated; CS= clinical study; Ref = reference; SIB = simultaneous integrated boost; V20 = volume receiving >20 Gy. All doses are given in Gy.
Respiratory gated SIB–IMRT, D. Majumdar, et. al.

Conclusion

Respiratory Gated (Breath hold) SIB–IMRT for breast cancer is feasible and is comparable with other treatment techniques. It reduces treatment duration by six fractions i.e. one week. It provides adequate PTV coverage. At median follow up of 8 months the skin toxicity and cosmesis are in excellent in high percentage of cases. It provides low ipsilateral lung dose. It provides low cardiac dose in left sided breast cancer patients. Boost volume is smaller if surgical clips are implanted during surgery.

References


