The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 10, July 2011
ISSN No. 2078-2101

The Official Journal of the Gulf Federation For Cancer Control

The Gulf Journal of Oncology

ISSUE 10 **JULY, 2011**

TABLE OF CONTENTS

Original Studies

Case Reports

Conference Highlights /Scientific Contribution

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

Introduction

Whole breast radiation is an integral component of Breast Conservative Therapy. It is apparent that an increase in local control improves breast cancer survival rate. The early breast cancer trial list collaborative group overview indicates that an absolute reduction in local recurrence at 5 years is associated in a 4:1 ratio with an absolute survival advantage at 15 years i.e. as a rule of thumb, every 4 local recurrences are avoided by RT prevents 1 death 15 years after diagnosis[1]. Therefore RT is expected to improve survival in subgroups where the absolute risk reduction for local recurrence is > 10%. Conventionally, radiotherapy to the breast is given by tangential fields for a period of 5-7 weeks, 5 fractions per week, one fraction daily[6]. Radiotherapy to whole breast to a dose of 45 Gy- 50 Gy (1.8

Correspondence: Dr. Saroj Kumar Das Majumdar, Head & Consultant Radiation Oncologist, Department of Oncology, Salmaniya Medical Complex, Manama, Bahrain. Email: sarojmajumdar@gmail.com rojs1@rediffmail.com

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[2, 3]. 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[4, 5]. Still, lesser number of indicated patients receive radiotherapy because referring physicians are scared of radiotherapy side effects[7]. 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 cosmoses due to dose inhomogeities. Compared to conventional tangential breast radiotherapy, IMRT is a treatment approach that reduces acute skin toxicity[8-11]. Early randomized data shows in favor of improved late cosmoses with IMRT for breast cancer[12] and also reduces the risk of normal tissue complication[13, 14]. 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 V-20 <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[15].

$$BED = D\,[1+d/(\alpha/\beta) - \gamma\, Tt/\alpha]$$

Where D = total dose.

d = the dose per fraction,

α,β = LQ parameters,
Tt = total treatment time in days,
$\gamma = \ln(2)/Tpot$, where Tpot is the potential doubling time.
Tpot= 15 days
$\alpha = 0.3$/ Gy
$\alpha/\beta = 10$ days (tumor)
$\alpha/\beta = 3$ 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[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

Study	Year	Tech	No. Cases	Breast Dose	Boost Dose	No.Fx	Mean Heart Dose	Ipsi-lateral Lung dose	Comment
BBCA (40)	2006	IMRT	5	50	None	25	12.8	15.1%	PS
UAB(41)	2007	IMRT	10	45	None	25	1.4-2.3	NR	PS
UPMC((42)	2007	IMRT	20	50	None	25	2.3	7.2%	PS
LOYOLA(20)	2006	SIB-IMRT	10	50.4	66.4	28	5.25	12.5%	PS
NYU(43)	2007	SIB-IMRT	91	40.5	48	15	2.0	1.3%	CS-Prone
NETHERLAND (44)	2007	SIB-3DCRT	30	50.7	64.4	28	4.8	5.5%	CS
EMORY (45)	2009	SIB-IMRT	356	45	59.92	28	2.6	10.6%	CS-165 Left
SMC	2010	SIB-IMRT	45	50.4	61.6	28	18.8	37.4%	CS

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

Abbreviations: fxs = 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.

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 = .0013), MLD (P = .016), and the location of tumor in the lower lobe (P = .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.

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 cosmoses 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

1. Clarke M, Collins R, Darby S, et al. effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15 –years survival: an overview of the randomized trials. *Lancet 2005*; 366:2087-2106.
2. Whelan T, Mac Kenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for woman with lymph node-negative breast cancer. *J Natl Cancer Inst. 2002*; 94:1143-1150.
3. START Titlists Group, Bentzen SM, Arawal RK, Aird EG, et al. The UK Standardisation of breast radiotherapy (START) Trial B of radiotherapy hypo fractionation for treatment of early breast cancer: a randomized trial. *Lancet. 2008*; 371:1098-1107.
4. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast conserving therapy of early breast cancer: 10 year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol.2007*; 25:3259-3265.
5. Romestaing P, Lehingue Y, Carrie C, et al. Role of 10 Gy boost in the conservative treatment of early breast cancer. Results of a randomized clinical trial in Lyon, France. *J Clin Oncol 1997*; 15: 963-968.
6. Ceilley E, Jagsi R, Goldberg S, et al. Radiotherapy for invasive breast cancer in North America and Europe: Results of Survey. *Int J Radiat Oncol Biol Phys 2005*;61:365-373.
7. Bckell NA, Le Par F, Wang JJ, Leventhal H. Lost opportunities; Physician reasons and disparities in breast cancer treatment. *J Clin Oncol 2007*; 25:2516-2521.
8. Mc Donald MW, Godette KD, Butker EK, Davis LW, Johnstone PAS. Long-term outcomes of IMRT for breast cancer: A single institute cohort analysis. *Int J Radiat Oncol Biol Phys 2008*; 72:1031-1040.
9. Pignol J, Olivotto I, Rakovitch E, et al. A multicentre randomized trial of breast IMRT to reduce acute radiation dermatitis. *J Clin Oncol 2008*; 26:2085-2092.
10. Freedman GM, Anderson PR, Li J, et al. IMRT decreases acute skin toxicity for women receiving radiation for breast cancer. *Am J Clin Oncol 2006*; 29: 66-70.
11. Harsola A, Kestin L, Grills I, et al. IMRT results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. *Int J Radiat Oncol Biol Phys 2007*;68:1375-1380.
12. Donovan E, Bleackley N, Denholm, et al. Randomized trial of standard 2D radiotherapy versus IMRT in patients prescribed breast radiotherapy. *Radiother Oncol 2007*; 82:254-264.
13. Hurkmans CW, Cho BCJ, Damen E, Zijp L. Mijnheer BJ.Reduction of cardiac and lung complication probabilities after breast irradiation using conformal radiotherapy with or without intensity modulation. *Radiother Oncol 2002*; 62: 163-171.
14. Bhatnagar AK, Brandner E, Sonnik D, et al.IMRT reduces dose to the contralateral breast when compared to conventional tangential fields for primary breast irradiation: Initial report. *Cancer J 2004*; 10: 381-385.
15. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol 1989*; 62:679-694.
16. Rose MA, Olivotto I, Cady B, et al. Conservative surgery and Radiation therapy for early breast cancer. Long-term cosmetic results. *Arch Surg 1989*; 124:153–157.
17. Gerber L, Lampert M, Wood C, et al. Comparison of pain, motion, and edema after modified radical mastectomy vs. local excision With axillary dissection and radiation. *Breast Cancer Res Treat 1992*; 21:139–145.
18. Kwa SL, Lévesque J V, Theuws JC, et al.Radiation pneumonitisasa function of mean lung dose: An analysis of pooled data of 540 patients. *Int. J. Radiat Oncol Biol Phys 1998*; 42: 1–9.
19. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria.*Invest New Drugs 1992*; 10:239 –253.
20. Rajanish S, Stephanie K, Kevin A, Steve C, Nesrin D, et al. *Medical Dosimetry. 2006*; 31:190-196.
21. Hong L, Hunt M, Chui C, et al. Intensity modulated tangential beam irradiation of the intact breast. Int. J. Radiat. *Oncol. Biol.Phys.1999*; 44:1155-64.

22. Taylor M.E., Perez CA, Halverson K.J., et al. Factors influencing cosmetic results after conservation therapy for breast cancer. *Int. J.Radiat.Oncol.Biol. Phys.1995*; 31:753-64.

23. Moody A.M., Mayles W.P., Bliss J. M., et al. The influence of breast size on late radiation effects and association with radiotherapy dose inhomogeneity. *Radiothera. Oncol. 1994*; 33: 106-12.

24. Vicini F A, Sharpe M, Kestin L, et al. Optimizing Breast Cancer treatment efficacy with intensity modulated radiotherapy. I*nt. J. Radiat.Oncl. Biol. Phys 2002*; 54:1336-44.

25. Ellen D, Natalie B, Erica D, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radioth. Oncol 2007*; 82: 254-264.

26. Pierce SM, Retch A, Lingos TI, et al. Long term radiation complications following conservative surgery (CS) and radiationtherapy (RT) in patients with early stage breast cancer. *Int J Radiat Oncol Biol Phys 1992*; 23: 915-923.

27. Krengli M, Sacco M, Loi G et al. *Int. J. Radiat Oncol. Biol. Phys. 2008*; 70:1460-1467.

28. Lind PAR, Wennberg B, Gagliardi G et al. Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. *Breast cancer research and treatment 2001*; 68: 199-210.

29. D. Oetzel, P. Schraube and F. Hensley, Estimation of pneumonitis risk in three-dimensional treatment planning using dose-volume histogram analysis, *Int J Radiat Oncol Biol Phys 33 (1995)*, pp. 455–460.

30. M.V. Graham, J.A. Purdy and B. Emami, Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC), *Int J Radiat Oncol Biol Phys 45 (1999)*, pp. 323–329.

31. I. Madani, K. De Ruyck and H. Goeminne, Predicting risk of radiation-induced lung injury, *J Thorac Oncol 2 (2007)*, pp. 864–874.

32. Hancock SL, Tucker MA, Hoppe RT, et al. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA 1993*; 270:1949-1955.

33. Marks LB, Yu X, Prosnitz RG et al. The incidence and functional consequences of RT – associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys. 2005*; 63:214-223.

34. Vernesi U, Banfi A, Salvadori B, et al. Breast conservation is the treatment of choice in small breast cancer. *Eur J Cancer 1990*; 26: 668-670.

35. Fisher B, Anderson S. Conservative surgery for the management of invasive and noninvasive carcinoma of the breast: NSABP trials. *World J Surg 1994*; 18:63-69.

36. Jacobson JA, Danforth DN, Cowan KH, et al: Ten year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *NEJM 1995*; 332:907-911.

37. Arriagada R, Le MG, Rochard L, et al. conservative treatment versus mastectomy in early breast cancer: pattern of failure with 15 years of follow up data. Institute Gustave –Roussy Breast Cancer Group. *J Clin Oncol 1996*; 14:1558-1564.

38. Pierce LJ, Strawderman M, Narod SA, et al. Effect of radiotherapy after breast- conserving treatment in women with breast cancer and germline BRCA1/2 mutations. *J Clin Oncol 2000*; 18:3360-3369.

39. Khan A J, Haffty BG. The location of contralateral Breast cancers after Radiation therapy. *The Breast Journal 2001*; 7: 331-336).

40. Popescu CC, Olivotto I, Patenaude VV, Wai ES, et al. Inverseplanned,dynamic, multi-beam, intensity-modulated radiationtherapy (IMRT): A promising technique when target volume is the left breast and internal mammary lymph nodes. *Med Dosim 2006*; 31:283–291.

41. Caudell JJ, De Los Santos JF, Keene KS, et al. A dosimetric comparison of electronic compensation, conventional intensity modulated radiotherapy, and tomotherapy in patients with early-stage carcinoma of the left breast. *Int J Radiat Oncol Biol Phys 2007*; 68:1505–1511.

42. Selvaraj RN, Beriwal S, Pourarian RJ, et al. Clinical implementation of tangential field intensity modulated radiation therapy (IMRT) using sliding window technique and dosimetric comparison with 3D conformal therapy (3DCRT) in breast cancer. *Med Dosim 2007*; 32:299–304.

43. DeWyngaert JK, Jozsef G, Mitchell J, et al. Accelerated intensity- modulated radiotherapy to breast in prone position: Dosimetric results. *Int J Radiat Oncol Biol Phys 2007*; 68: 1251–1259.

44. Van der Laan HP, Dolsma WV, Maduro JH, et al. Three-dimensional conformal simultaneously integrated boost technique for breast-conserving radiotherapy. *Int J Radiat Oncol Biol Phys 2007*; 68:1018–1023.

45. McDonald M W, Godettekd, Daisy J et al Three –year outcomes of Breast Intensity Modulated Radiation Therapy with Simultaneous Integrated Boost. *Int. J. Radiation Oncology Biol. Phys. 2009*, pp. 1–8.

Contact :
The Gulf Federation for Cancer Control
P. O. Box 26733 Safat 13128 Kuwait
Tel. (00965) 22530186 / 22530184 Fax: (00965) 22510137
website : http://www.gffcc.org
email : gffccku@yahoo.com

Electronic Edition
www.gffcc.org/journal