

Localisation of tumor bed and its impact on dosimetry for tumor bed boost irradiation in patients treated with breast conserving surgery using different techniques

Principal Investigators: Dr. Ashwini Budrukkar

Co-Investigators:Dr.ArbaazPatwe

Dr.TabassumWadasadawala

Dr. Rajiv Sarin

Dr. Rakesh Jalali

Dr.Santam Chakraborty

Mr.RiturajUpreti

Mrs.UditaUpreti

Introduction:

For patients with early stage invasive disease, surgery can either be a breast conserving resection of the primary tumor or a mastectomy. Several randomised prospective clinical trials have indicated that breast conserving surgery with whole breast radiation provides long term outcomes equivalent to those of mastectomy^{1,2,3,4}. The goal of breast conserving surgery is to remove the primary tumor with surgical margins that are free from invasive or insitu disease. A secondary goal is to provide the best possible cosmetic outcome without retraction, nipple displacement, or excess volume loss from the procedure. For some women with larger breasts, oncoplastic surgery can be used in which local tissue rearrangements are performed at the time of surgical resection to maintain optimal breast aesthetics

Radiation is essential component of breast conserving therapy. The use of RT improved recurrence free, breast cancer specific survival and overall survival in both patients with negative and positive axillary lymph nodes in the most recent metaanalysis of Early Breast Cancer Trialists Collaborative Group (EBCTCG)⁵ which included trials begun before 2000. It included data from 42080 patients with breast cancer treated in 78 clinical trials that investigated locoregional treatments between 1952 and 1995. Among those patients were 7311 patients treated in 10 trials comparing radiation vs no radiation after breast conserving surgery and 9933 patients treated in 25 trials comparing radiation vs no radiation after modified radical mastectomy. In the trials that investigated radiation as a component of breast conserving therapy, radiation was shown to reduce the risk of local recurrence by two thirds and to improve the absolute 15 year overall survival rate by 6% (41% versus 35%). Similarly for patients with positive lymph nodes treated with modified radical mastectomy, radiation reduced the risk of locoregional recurrence rate by 21% at 15 years (29% versus 8%), which was associated with a 5% decrease in the 15 year breast cancer mortality rate (60% versus 55%). A more recent update of the analyses continues to demonstrate locoregional and survival advantages for radiation therapy

Even if surgical margins are negative after BCS, 30-40% risk of microscopic tumor cells in tumor bed. Most recurrences (65-80%) are located in vicinity of tumor bed as shown in EORTC⁶ trial and NSABP-06 trial. It is therefore important to ensure the tumor bed lies well inside the treatment volume encompassed by tangential fields to whole breast and subsequent tumor bed boost. There is also a pathological basis for giving boost to tumor bed-residual tumor foci have been reported in 1-2 cm in around 20-25% patients/histopathological specimens.

The EORTC 22881-10882⁷ trial studied the effect of addition of a boost dose on the primary tumor bed after lumpectomy in breast conserving treatment for breast cancer. It included 5318 patients who received whole breast irradiation after lumpectomy and then randomised to boost of 16 Gy to tumor bed or no boost. The median follow up was 10.8 years. It was found that 47% of local recurrences were in primary tumor bed, 10% in scar, 29% outside original tumor area and 13% were diffuse. At 10 years, the cumulative incidence of local recurrence was 10.2% versus 6.2% for the 0 Gy and the 16 Gy boost groups (p< 0.0001).

Regarding surgical techniques for BCS, two main methods can be distinguished: open cavity and closed cavity technique. In the former only the superficial part of the cavity is closed allowing the formation of seroma. During closed cavity technique a full thickness closure is performed by suturing the deep and superficial layers of the surrounding breast tissue. In this case seroma does not develop and the target volume definition can be much more difficult.

Oncoplastic surgery represents a special form of closed cavity breast conservation tumorsurgery. The advantage of oncoplastic surgery is the combination of tumour excision and immediate reconstructive surgery. Because of the excellent cosmetic results oncoplastic surgery has become more frequent in the past years. However adjuvant radiotherapy procedures have to face the possibility of breast tissue displacements at risk of residual tumor cells, influencing the post operative target definition for partial breast irradiation

The tumor beds of medially and laterally located tumors are particularly prone to underdosage if surface landmarks are used as fiducial points for whole breast RT planning. It is therefore very important to localise the tumor bed even for whole breast RT planning. Clinical planning of tumor bed boost volume based on preoperative imaging, surgical note and breast scar position is very unreliable. Increasingly the breast scar is placed often some distance from the tumor for wire guided localisation biopsy or better cosmetic outcome. In addition the practice of oncoplastic surgery where breast tissue is repositioned following wide excision to minimise the surgical deficit is becoming standard of care. In this situation the preoperative imaging bears very little final relation to tumor bed.

Computed tomography and ultrasonography can use the seroma as a surrogate for tumor bed position, but there are limitations. First, the seroma is only clearly defined in only about quarter of patients. Second the seroma underestimates the tumor bed defined by implanted clips.

Uncertainty in localising the tumor bed in medial or lateral tumors can be overcome by increasing the posterior field borders of whole breast tangents, but only at expense of increased morbidity of ribcage and lung, and potential mortality in women with left sided tumors. The heart is the most sensitive organ, a few Gy being associated with risk of heart disease and every effort needs to be made to exclude the organ from treatment volume. When localising the tumor bed boost, increasing the clinical target volume is a crude way of avoiding geographical miss. This is particularly important in the era of oncoplastic surgery when the tumor bed may be well away from its primary location.

Accurate delineation of the target volume is of utmost importance while delivering tumour bed boost with external beam radiotherapy. Different institutions use different methods for delineation of the tumour bed.

Clinical history and patients' recollection of tumour position, clinical photographs, tattoos, surgical scar, mammography, surgical clips, ultrasonography, Computerized tomography

(CT) scan and Magnetic resonance imaging (MRI) are the commonly utilized techniques. Many a times, a combination of one or more of these techniques is considered while delineating the tumour bed boost.

Amongst all the randomised trials assessing role of radiotherapy boost, surgical clips were used in all patients for assessing boost volume only in the Budapest trial⁸. In other studies, the boost volumes were usually defined on clinical and surgical details. It was hypothesized that increasing differences between local failure rates in whole breast radiotherapy (WBRT) arm versus WBRT+boost arm in Lyon trial (4.5% vs. 3.6%), EORTC trial (10.2% vs. 6.2%) and Budapest trial (15.5% vs. 6.7%) [may well have been due to the different techniques of tumour bed delineation as the difference in boost doses between all these trials were not significantly different. Hence an accurate delineation of tumour bed is important as it may translate into improved local control rates.

Tumor bed localisation and open or closed cavity BCS:With superficial closure, only the superficial aspect of the cavity is closed, allowing the formation of a seroma to prevent deformation of the breast. A full-thickness closure consists of repositioning of the surrounding breast tissue and suturing the deep and superficial layers, preventing the development of significant seroma. There is a paucity of data on the influence of surgical closure techniques on EB treatment planning. It can be hypothesized that superficial closure may lead to a better-delineated cavity as a well-visualized seroma has been shown to decrease interobserver variations nevertheless, it may also lead to a larger treatment volume and greater late toxicity effects. However, with full-thickness closure, the surgical clips may be displaced with the approximation of the surrounding breast tissue and not correlate with the true extend of the cavity. In a recently published single institutional experience, Shaikh et al.⁹ did not find statistically significant difference in mean cavity visualization scoring (CVS) (Smitt et al¹⁰, 1 = no visible cavity, 2–4 = heterogeneous cavity with indistinct, distinct, or clearly defined margins, 5 = homogenous cavity with clearly defined margins) or normal tissue dosimetric endpoints between 29 patients who underwent superficial closure and sixteen patients who underwent full-thickness closure. A higher percentage of patients who underwent superficial closure had CVS scores >2 (79% vs. 63%). The small patient numbers in each cohort and its retrospective nature are the limitations of the study.

Oncoplastic BCS techniques with parenchymal rearrangement present new challenges to the localisation of the tumour bed and therefore delivery of local boost radiotherapy. Although use of whole-breast radiation therapy (RT) is straightforward, difficulties in localization of the tumor bed for the local RT boost have not been investigated.

Pezner et al¹¹ carried out a retrospective review of 25 patients who received RT after breast conservation surgery with oncoplastic reconstruction. It was found that among 11 patients with a minimum of 4 surgical clips placed at tumor resection, 8 (73%) had the final tumor bed extend beyond the original breast quadrant or be completely relocated into a different

region. In 3 (27%) cases, the clinical treatment volume was 2 to 3 separated regions within the breast.

Thus, in breast cancer patients who have undergone oncoplastic surgery, the tumor bed is frequently more extensive and possibly more relocated compared to original presentation. Placement of surgical clips after tumor resection and before oncoplastic reconstruction may be the most accurate method to localize the RT local boost field^{12, 13}.

Techniques of Radiotherapy boost delivery-Variou techniques of tumor bed boost delivery have been extensively studied and their efficacy compared retrospectively and prospectively. The various techniques are electrons, photons(less commonly used due to higher penetration and increased doses to critical underlying structures) and interstitial brachytherapy (i.e. interstitial placement of needles into tumor bed either intraoperatively or postoperatively)

With most of the centres now having linear accelerators, coronal en face electron beams have now become standard practice in most institutions. Minimal dose to underlying normal structures, i.e. lung and breast to the maximum, varying energy of electrons, feasibility of defining field on skin, an outpatient procedure with minimal patient discomfort make it a favourable option for both the patient as well as treating radiation oncologist. Most commonly used energies are 9-12 MeV. However, the boost fields defined on the basis of clinical details have been found to be erroneous in several studies. Hence, the dimensions as well as depth for tumour bed boost should be determined either by fluoroscopy or CT combined with surgical clips, or an ultrasound. The most common prescription isodose for electron boost delivery is 90-95% isodose. But, in an organ such as breast with multiple edges and curvatures in different axes, the prescription isodose may not cover the whole target volume uniformly. This problem is commonly seen when tumours are located at areas where there is a sudden change in the depths like inframammary and axillary folds. The depths of soft tissue vary greatly in these areas and uniform energy electron beam may either underdose the tumour bed, or deliver higher dose to underlying normal structures. The electrons have limited role in patients with large breasts, tumours situated at a depth i.e. closer to heart (on left) and lungs and in folds. CT based planning in three dimensions may help to determine the dose distributions accurately and help in choosing the optimal energy.

The margins to be given to tumour bed for defining boost field have also been discussed. Harrington et al¹⁴ have shown that a boost field marked on the basis of clinical data and background with a margin of 2 cm all around covers radiological field with same margin in only 1/3rd (33%) of patients. Although Vicini et al. showed that a margin of 1 cm around the tumour covers microscopic disease adequately, in EORTC trial margins of 1.5 cm were given for microscopically completely excised tumours. Overall, a margin of 1.5-2 cm to the tumour bed has been reported to cover all subclinical disease in patients with clear microscopic margins.

Some institutions have practised tumour bed boost by 4-6 MV photons. The practice of delivering boost by photons has declined after widespread availability of electrons due to

higher penetration and increased doses to underlying critical structures. Photons can be used in patients with small tumour bed as late term sequelae of electrons such as telangiectasia may not be acceptable to some patients treated with electrons.

Aims and Objectives: Primary objective- To evaluate dosimetric outcomes in tumor bed boost irradiation in patients undergoing breast conservative surgery using three different surgical techniques

Secondary objective-Evaluation of cosmesis in patients prior to radiotherapy, at the time of completion of radiotherapy and 6 months post completion of radiotherapy

Material and methods-

Patients will be screened for the study at the time of radiotherapy simulation for External beam radiotherapy

The sample size has not been calculated as this is a pilot study. Twenty patients will be accrued for the purpose of this study. The patients will be divided into three groups:

Group A- Patients who underwent open cavity BCS

Group B- Patients who underwent closed cavity BCS

Group C- Patients who underwent oncoplasty

Inclusion Criteria- All patients undergoing Breast Conservative Surgery (Open Cavity/Closed Cavity) or Oncoplasty will be eligible for this study.

Exclusion Criteria-1. Patients undergoing Neoadjuvant chemotherapy will not be eligible for the purpose of this study.

2. All patients undergoing Modified Radical Mastectomy will not be eligible for the purpose of this study

Informed consent will be taken for all patients at the time of Radiotherapy simulation. All patients will first receive external beam Radiotherapy to the whole breast to a dose of 40Gy/15#/3weeks. The patients will then be planned for boost radiation to the tumor bed to a dose of 12.5 Gy/5#.

The combination of surgical clips with a treatment planning CT scan for the lumpectomy site for electron boost and to determine the appropriate energy will be used for tumour bed boost delineation

For the boost planning CT scan a small thermocol wedge will be used, with a pillow under the shoulder to make the surface as flat as possible.

The pT size in HPR of lumpectomy plus a margin of 2 cm in all directions is the approximate size of the boost field. The margins of this field are marked on the skin with the centre of scar as the center of the field and copper wire is placed on the markings.

5 mm slice thickness CT scan will be taken in the treatment position. After the scan acquisition the data will be transferred to the Varian Eclipse treatment planning system.

The post-operative cavity depicted on the CT images will be contoured section by section. All available images will be assigned a cavity visualisation score⁹ (CVS) as per the British Columbia Cancer Agency Cavity visualisation score 0-No visible seroma, 1-scar/shadow, 2-seroma identifiable but with significant (>30%) uncertainties, 3-seroma identifiable with minor (<30%) uncertainties, 4- seroma easily identifiable, generally homogenous with some blurring of margin, 5-seroma clearly identifiable, homogenous with sharp boundaries. The mean cavity visualisation score will be determined for each group of patients.

The CTV will be generated by using a 15 mm uniform expansion from the lumpectomy cavity but limited by skin and chest wall. The CTV will be extended by an additional 10 mm uniform expansion to generate the PTV

Treatment plans for tumor bed boost irradiation will be made using both electrons and photons with 3DCRT technique for each patient and comparison will be made for various dosimetric variables. The photon beam plan will only be generated for purposes of dosimetric study and will not be used for treatment of the patients

The following dosimetric variables will be determined for each patient -seroma cavity volume (ccs). PTV volume (ccs). In addition the ratio between the PTV volumes to the whole breast volume will be determined. The Radiation Conformity Index (RCI) will be determined for both set of plans. It was first defined by Knoos et al and a revised definition appeared in ICRU 62 It is the ratio of volume of the PTV to the volume that receives 95% prescribed dose or higher ($RCI = V_{PTV} / V_{95\%}$). The Dose Homogeneity Index (DHI) will be determined for both set of plans (DHI). It is ratio of dose received by 95% of PTV volume to the dose received by 5% of PTV volume ($DHI = D_{\geq 95\%(\text{within PTV})} / D_{\geq 5\%(\text{within PTV})}$). The dose received by several normal structures will be determined for both set of plans-normal ipsilateral breast tissue (Whole breast volume- PTV volume), contralateral breast, ipsilateral lung, contralateral lung and heart

The borders of the portal will be modified based on the position of the lumpectomy cavity/seroma of the scan and marked on the patient. The boost irradiation for all patients will be done using electrons. The energy of electrons required will be decided from the depth of the lumpectomy cavity.

In addition the cosmesis will be determined for all the patients prior to starting radiotherapy, at the time of conclusion of radiotherapy and 6 months post completion of radiotherapy. This will be done by using the criteria suggested by Harris et al

1. Excellent: the treated breast almost identical to the untreated one.
2. Good: the treated breast slightly different from the untreated breast.
3. Fair: obvious difference between the two sides without major distortion.
4. Poor: the treated breast is seriously distorted.

Statistical analysis shall be performed with the Statistical Package for Social Sciences (SPSS, Chicago, IL) software package, version 21.0, for Windows A two-tailed PValue less than 0.05 will be considered as statistical significance in this study. Descriptive statistics, including frequency distributions, means \pm SD, and 95% confidence intervals, to be calculated for demographic and treatment variables. The statistical analysis will be carried out using the One way ANOVA or Krsukal Wallis test and categorical comparison will be done using Chi Square test.

References:

- [1] Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–32.
- [2] Arriagada R, Le MG, Rochard F, et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol* 1996;14:1558–64.
- [3] Blichert-Toft M, Nielsen M, Duing M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008;47:672–81.
- [4] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233–41.
- [5] Early Breast Cancer Trialists' Collaborative Group. Radiotherapy for early breast cancer. *Cochrane Database Syst Rev* 2002;2:CD003647.
- [6] Collette L, Fourquet A, Horiot JC, et al. Impact of boost dose of 16 Gy on local control in

patients with early breast cancer: The EORTC “Boost versus no boost” trial. *RadiotherOncol* 2000;56(Suppl. 1):46

[7]Bartelink H, Horiot JC, Poortmans P, Struikmans H, Bogaert WV, Barillot I, et al. Impact of radiation dose on local control, fibrosis and survival after breast conserving treatment: 10 years results of the EORTC Trial 22881-10882. San Antonio Conference, 2006

[8]Polgar C, Orosz Z, Fodor J, Major T, Mangel L, TakacsNagy Z, et al. The effect of tumour bed boost on local control after breast conserving surgery. First results of the randomized boost trial of the National Institute of Oncology. *MagyOnkol* 2001; / 45: / 385-91.

[9]Shaikh T, Narra V, Goyal S, et al. Lumpectomy closure technique does not affect dosimetry in patients undergoing external-beam-based accelerated partial breast irradiation. *Ann SurgOncol* 2013;20:1323–8.

[10]Smitt MC, Birdwell RL, Goffinet DR. Breast electron boost planning: comparison of CT and US. *Radiology* 2001;219:203–6.

[11]Pezner RD, Tan MC, Clancy SL, et al. Radiation therapy for breast cancer patients who undergo oncoplastic surgery: localization of the tumor bed for the local boost. *Am J ClinOncol* 2013

[12] Yang Z, Chen J, Hu W, et al. Planning the breast boost: how accurately do surgical clips represent the CT seroma? *RadiotherOncol* 2010;97:530–4.

[13] Goldberg H, Prosnitz RG, Olson JA, et al. Definition of postlumpectomytumor bed for radiotherapy boost field planning: CT versus surgical clips. *Int J Radiat OncolBiolPhys* 2005;63:209–13.

[14]Harrington KJ, Harrison M, Bayle P, et al. Surgical clips in planning the electron boost in breast cancer: a qualitative and quantitative evaluation. *Int J Radiat OncolBiolPhys* 1996;34:579–84.

[15]Vicini FA, Kestin LL, Goldstein NS. Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: A pathologic analysis. *Int J RadiatOncolBiolPhys* 2004; / 60: / 722-30.

