Adjuvant Radiation Therapy for Breast Cancer

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Abstract

The objective of adjuvant radiation therapy (RT) is to eradicate any tumor deposits following surgery for patients treated by either breast conserving surgery or mastectomy. Radiotherapy reduces the risk of local relapse and reduces breast cancer mortality. There have been significant advances in radiotherapy technology, with sophisticated imaging integrated into planning systems using techniques that protect the heart with shielding or deep inspiration breath holding (DIBH). Modern intensity modulated radiotherapy (IMRT) or volumetric modulatedarc therapy (VMAT) techniques can be used to shape the dose distributions around the heart in order to reduce the high-dose volume. Nevertheless, this is usually at the cost of a low-dose spill to the lungs, the contralateral breast and the whole heart. Breast-conserving therapy (BCT) for early-stage breast cancer has a survival rate comparable to mastectomy, therefore BCS and radiation have become the standard treatment for stage I–II breast cancer. After BCS, radiation therapy in the form of Whole Breast Radiation Therapy (WBRT) is the standard adjuvant treatment, with 90–95 percent local control rates. After breast conserving surgery, radiation can reduce the chance of recurrence.

Keywords: Adjuvant Radiation Therapy, Breast Cancer

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Introduction:

The objective of adjuvant radiation therapy (RT) is to eradicate any tumor deposits following surgery for patients treated by either breast conserving surgery or mastectomy. Radiotherapy reduces the risk of local relapse and reduces breast cancer mortality *(1)*.

Types and schedules of external beam radiation:

There are 2 main types of breast irradiation:

- **Conventional radiation therapy:** The standard schedule for breast radiation has been6-7 weeks consisting of 45–50Gy in 25 fractions of 1.8 or 2Gy/day, 5 days a week then boost 10-16Gy over 5-8.
- **Hypofractionated radiation therapy:** In this approach, radiation is given in larger doses and fewer sessions. It might also lead to fewer short-term side effects *(2).*

The first important challenging step in the RT technique came with the introduction of the CT-based treatment planning and 3D conformal RT (3DCRT) that provides us precise target volume definition, dose distribution calculation, and virtual simulation. Optimal shielding of organs at risk (OARs), including the heart, lungs, brachial plexus, esophagus, trachea, thyroid, and spinal cord decreased normal tissue exposure. Additionally, more homogeneous dose distribution in the clinical target volume could be obtained *(3).*

There have been significant advances in radiotherapy technology, with sophisticated imaging integrated into planning systems using techniques that protect the heart with shielding or deep inspiration breath holding (DIBH). Modern intensity modulated radiotherapy (IMRT) or volumetric modulatedarc therapy (VMAT) techniques can be used to shape the dose distributions around the heart in order to reduce the high-dose volume. Nevertheless, this is usually at the cost of a low-dose spill to the lungs, the contralateral breast and the whole heart *(4).*

IMRTis an advanced form of 3DCRT that became increasingly available for breast cancer. Several important studies have been carried out on the use of IMRT for breast cancer patients requiring complex breast treatments. Patients with larger breasts are more likely to have dose inhomogeneities and most likely to benefit from IMRT. It can also be the best alternative for left-sided breast cancers to decrease cardiac dose, re-irradiation, contralateral breast irradiation, partial breast irradiation(PBI), and deeply seated tumor bed irradiation.The major goal for IMRT technique is providing more homogenous dose distribution throughout the breast and concave structures such as the chest wall. This technology also allows better conformality of dose to the target and better sparing of OARs compared to non-IMRT plans *(3).*

VMAT can achieve highly conformal dose distributions by rotating the linear accelerator gantry at varying speeds through one or more arcs, while simultaneously changing the field shape. This allows shaping or sculpting radiation doses to complex cancer volumes while using modern equipment with on-board CT scans, with treatment times of about five minutes, to reduce the dose to normal structures such as the heart. These advances are likely to further improve the incremental benefit of radiation over and above surgery and systemic therapy and thus increase survival rates.Patients who receive hypofractionated radiation with VMAT are less likely to develop

radiotherapy(RT)-related complications than those receiving conventional RT.To reduce unwanted irradiation on the lung, the method uses partial rotation treatment*(5)*.

Helical TomoTherapy is a technique where IMRT is administered to a patient in motion along the rotation axis of a megavoltage X-ray source, offering unique 360-degree rotational irradiation. This rotational-delivery approach around a single "virtual isocenter" may avoid the uncertainties inherent in multiple patient shifts. It presents dosimetric advantages compared to 3D-CRT with regards to coverage of the target volumes, sparing the OAR with acceptable clinical tolerance, especially for patients with challenging anatomy or bilateral breast treatment. Furthermore, with HT there is no need to irradiate the nodal groups separately from the ipsilateral breast enabling the delivery of continuous craniocaudal irradiation along the entire extent of the disease, which reduces junction problems *(6)*.

Phase III, randomized controlled trial, TomoBreast, indicate post-surgery hypofractionated radiotherapy delivered with the TomoTherapy System is superior to conventional radiotherapy in preserving long-term heart and lung functioning in women with early breast cancerenabling them to more easily perform daily and leisure time activities, and/or work. An analysis of patient reported outcomes showed 10-year survival free of heart and lung deterioration was 84.5% with TomoTherapy delivered radiotherapy - a significant improvement above the 66.9% achieved with conventional radiotherapy.

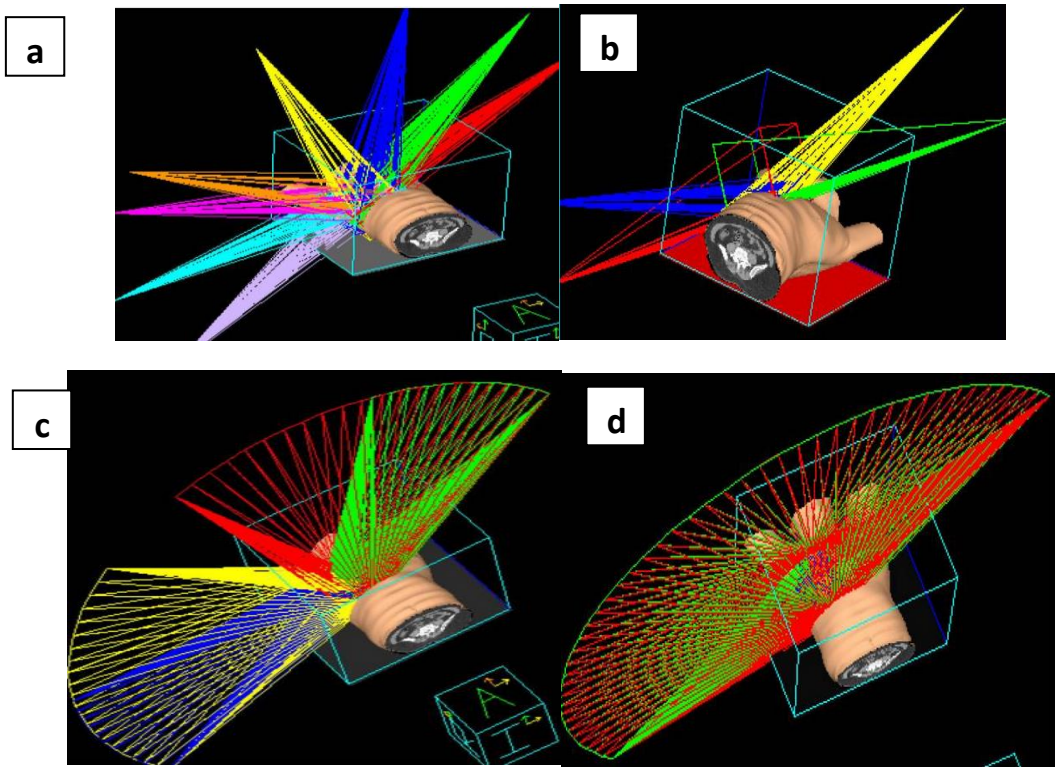

Fig.(1): Treatment planning using (**a**) intensity-modulated radiotherapy (IMRT), (**b**) hybrid 3D conformal radiotherapy (3D-CRT)/IMRT, (**c**) non-continuous partial arc, and (**d**) continuous partial arc*(5)*.

Timing of radiotherapy:

Delaying the initiation of radiotherapy up to 32 weeks, for administration of long-course chemotherapy, does not compromise patient outcomes. No increased risk of local failures in patients delaying their radiation therapy until after systemic treatment.Radiotherapy should be started within 12 weeks of the last date of surgery or last cycle of planned adjuvant chemotherapy *(7).*

Postmastectomy radiation therapy:

Definite indications for chest wall radiotherapy post mastectomy are *(8):*

- 4 or more involved axillary lymph nodes
- Tumor size greater than 5cm
- Involved excision margins
- The presence of 2 or more of the following minor risk factors:

– 1-3 involved axillary lymph nodes

– Grade 3

– Lympho-vascular invasion

– Young age 35 or less.

Axillary radiotherapy is considered in the following situations:

1) Positive axilla following the sampling of more than 4 lymph nodes.
2) Positive sentinel lymph node biopsy as an alternative to axillary clearance.
3) NX (no surgical data available or in-proper dissection) *(9)*

Supraclavicular fossa is considered in the following situations:

1) Four or more axillary nodes contain metastatic disease.
2) The extent of nodal disease is unknown or uncertain because the axilla either has not been treated surgically or the surgery has been suboptimal *(9).*

Internal Mammary Chain:Not routinely treated.

Within the radiation field, locoregional recurrence was defined as the breast and supraclavicular region, and a definitive diagnosis was established by clinical and imaging investigations. In patients with breast cancer and more than 10 axillary lymph node metastases, axillary or supraclavicular recurrence was the most common locoregional recurrence pattern. As a result, in patients with a

high number of axillary lymph node metastases, modification of the supraclavicular field to include the entire axilla should be considered ***(Yu et al., 2016).***Even in patients with good prognostic characteristics (pN0, ER-positive, low grade), omission of RT should only be considered in the presence of comorbidities that result in a significant reduction in life expectancy***(10).***

Radiation Therapy in Breast-Conserving Therapy:

Early-stage breast cancer is frequently treated with breast-conserving therapy (BCT), which includes a lumpectomy followed by whole-breast radiation therapy to remove any leftover tumor in the remaining breast tissue.Breast-conserving therapy (BCT) for early-stage breast cancer has a survival rate comparable to mastectomy, therefore BCS and radiation have become the standard treatment for stage I–II breast cancer.After BCS, radiation therapy in the form of Whole Breast Radiation Therapy (WBRT) is the standard adjuvant treatment, with 90–95 percent local control rates.After breast conserving surgery, radiation can reduce the chance of recurrence and breast cancer death ***(11).***

Omission of radiation therapy after breast-conserving surgery should be an option for older patients with localized, HR-positive breast cancer who are receiving adjuvant hormone therapy and meet certain clinicopathologic criteria, as patients aged 65 or older with hormone receptor (HR)-positive breast cancer who did not receive radiation therapy after breast-conserving surgery had similar 10-year survival rates when compared to patients who received postoperative radiation therapy, according to updated 10-year data from the PRIME II study. Multiple international trials have clearly demonstrated the efficacy of breast-conserving surgery followed by radiation therapy for early invasive breast cancer. Patients who did not receive whole-breast radiation after breast conserving surgery had higher recurrence rates and a pattern of recurrences that occurred predominantly in the tumor bed in these randomized studies ***(12).***

For patients with clinically node-negative breast cancer undergoing sentinel lymph node SLN biopsy who were found to have nodal involvement, the previous standard of care had been to proceed to ALND. However, several landmark trials have changed this paradigm. The AMAROS trial randomly assigned patients to completion ALND or axillary radiation in those patients with a positive SLN. At 10 years, no difference in locoregional recurrence (LRR) was noted with reduced toxicities seen with axillary RT. Similarly, the ACOSOG Z011(Alliance) trial randomly assigned patients to ALND or SLND. Although the trial did not allow for the use of a third field of radiation (ie, regional nodal treatment), review of the study found substantial use of high tangent radiation to cover the lower axilla or the use of a third field. The 10-year rates of overall survival in the SLND alone and ALND groups were 86.3% and 83.6%, respectively, compared with 82.8% in the nodal irradiation group in MA.20 and 82.3% in EORTC 22922/10925, suggesting that the ACOSOG Z0011 eligibility criteria identified a population that may not benefit from comprehensive nodal irradiation. Thus, although nodal irradiation may be added to the management of some patients with node-positive tumors based on an evaluation of their overall risk profile ***(13).***

Taken together, these data support the use of axillary radiation in lieu of ALND in patients with one to three sentinel nodes involved and can be considered for patients undergoing breast conservation or mastectomy. In patients with a micrometastasis on SLN biopsy, the long-term outcomes from the IBCSG 23-01 study confirmed that ALND can be omitted. In those patients undergoing ALND, with four or more nodes involved and those with extracapsular extension commonly offered Regional nodal irradiation (RNI) that can include the dissected axilla, supraclavicular fossa, and/or the internal mammary nodes. In patients with one to three nodes involved the role of RNI is controversial. Outcomes from the Early Breast Cancer Trialists Group meta-analysis confirmed the benefit of adjuvant RT (including RNI) in patients with one to three nodes involved after axillary dissection, even demonstrating a benefit with a single node involved. However, concerns have existed regarding whether this holds true with current surgical and systemic therapy approaches *(13).*

However, modern data have found the results to be consistent with the results of the MA20 trial supporting the use of RNI; the trial randomly assigned patients (85% with one to three nodes involved after ALND to RNI or not following BCS. Long-term outcomes demonstrated that the addition of RNI was associated with a reduction in LRR and distant metastases with estrogen receptor–negative patients having an overall survival advantage; similar results were seen in a multi-institutional modern analysis as well. As such, RNI can be considered for all patients with macrometastatic nodal involvement following ALND. Planning for RNI in this population may involve blocking the dissected axilla (therefore reducing dose to the axilla and potentially lymphedema rates) while incorporating the supraclavicular fossa and/or the internal mammary nodes *(13).*

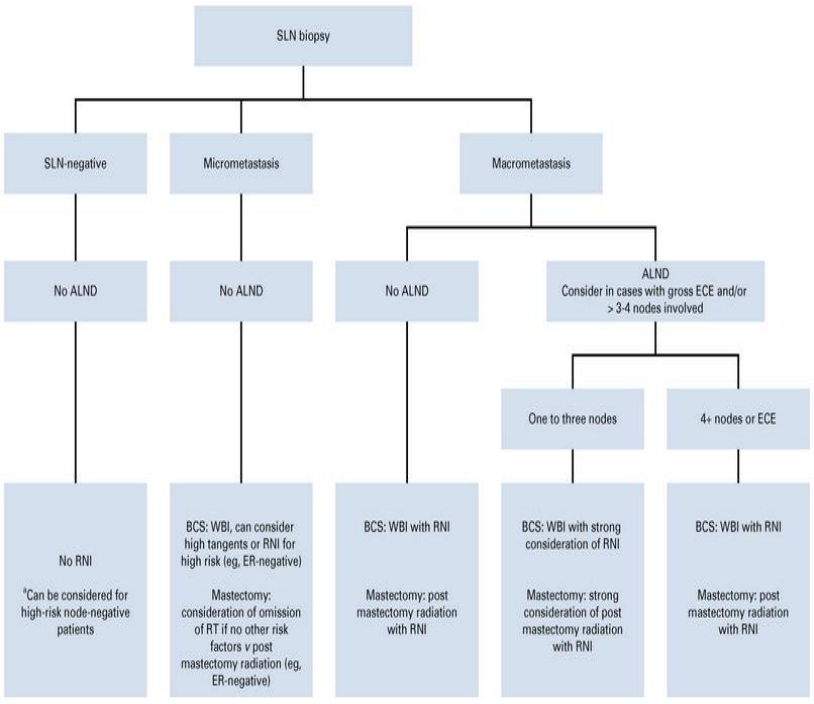

Fig.(2): Treatment of regional lymphnodes, SLN, ALND and RNI *(13).*

WBRT alone reduces the chance of any initial recurrence (both locoregional and distant) by 15% over 10 years and the risk of breast cancer-related mortality by 4% over 15 years ***(11).***The addition of a radiation boost reduces the recurrence rate (RR) by another 50%.According to ***Bartelink et al.***, ***(14)*** the 20-year cumulative incidence of ipsilateral breast tumor recurrence in the no boost group was 16.4 percent against 12 percent in the boost group ***(14).***

As a result, administering an extra dose to the tumor bed was justified in order to improve local control.Most patients who have unfavourable risk factors for local control, such as age 50 years, grade 3 tumors, lymphovascular invasion, hormone receptor negativity, or extensive intraductal component, and non-radical tumor excision (focally—otherwise, additional surgery should be done) should receive Boost ***(14).***

In early-stage breast cancer patients, shortening the treatment period contributes to increased economic feasibility and patient satisfaction. If the same treatment effect can be obtained at a lower cost, it can be said to be a more efficient treatment. For patients who have to go to the hospital from long distances, it is also advantageous in terms of the saving time required for commuting to the hospital. Hypofractionated RT is superior to conventional RT in terms of cost-effectiveness and time saving.Thus, many breast cancer patients prefer hypofractionated RT. Conventional radiotherapy, which consists of 45–50 Gy in 25 fractions of 1.8 or 2 Gy/day, 5 days a week, followed by a boost of 10-16 Gy over 5-8 days, may lead to patients avoiding complementary treatment after conservative surgery or abusing radical mastectomy in the early stages, resulting in undertreatment or overtreatment in many cases.It would also contribute to a significantly more efficient use of resources and time in some busy Radiation Oncology departments, resulting in increased cost and logistical burden.Recent randomised trials have shown that hypo-fractionated whole-breast irradiation is equal to more traditional whole-breast irradiation in terms of local recurrence, toxicity and cosmetic outcome ***(15).***

Biologically, it is known that good treatment results can be obtained when hypofractionated RT for breast cancer is performed because the estimated alpha/beta value of breast cancer is 3.6Gy according to a previous radiobiologic report by ***Yarnold et al.(16)*** An α/β value of around 3Gy for late normal tissue changes in the breast is derived from the estimated equivalence of 41.6Gy in 13 fractions and 50Gy in 25 fractions over 5 weeks, in line with trial predictions ***(16).***Assuming a typical α/β value of 3.0Gy for late normal tissue responses, a 15-fraction regimen reproducing the effects of 25 fractions of 2.0Gy requires a reduction in total dose from 50 to 42.8Gy in fractions of 2.85Gy. The linear-quadratic model predicts that the Ellis formula estimate of 45Gy in 15 fractions is equivalent to 54Gy in 2.0Gy fractions ***(17).***

Regarding radiation dose, the UK Standardization of Breast Radiotherapy (START) B trial6 showed that various hypofractionated radiation doses (2.7–3.3 Gy/fraction) were as effective as standard conventional RT doses (1.8–2 Gy/ fraction) ***(18).***

Table(4): Equivalent Dose (EQD2) ***(19).***

Normal tissue responses	α/β ratio (Gy)	EQD2 (Gy) Conventional 50 Gy/25 fractions	START B 40 Gy/15 fractions	OCOG 42.5 Gy/16 fractions	Gupta et al. Trial 36.63 Gy/11 fractions
Fibrosis	2.0	50	46.8	49.6	48.8
Contracture	3.5	50	44.9	47.7	45.5
Telangiectasia	4.0	50	44.5	47.2	44.7
Desquamation	11.0	50	42.1	44.7	40.4
Locoregional tumor control	α/β ratio (Gy)	WBI + boost 10 Gy/5 fractions	WBI + boost 10 Gy/5 fractions*	WBI + boost 10 Gy/4 fractions*	WBI + boost 13.32 Gy/4 fractions
Tumor	4.0	60	54.5	58.1	61.0

This hypofractionated technique is based on a radiobiologic model in which a greater dosage per fraction is delivered in fewer fractions (usually with a lower total nominal dose) throughout a shorter overall treatment time that is at least as effective as the traditional lengthier schedule.It is a well-established treatment option after breast-conserving surgery for a restricted subset of early breast cancer patients ***(20).***

No differences in local recurrence, loco-regional recurrence, disease-free survival, and overall survival rates were observed between moderately hypofractionated irradiation and conventional radiation doses groups. The rate of severe side effects was low in both groups; acute and late side effects and cosmesis are comparable or tend to be lower after moderately hypofractionated irradiation than after conventional radiation doses ***(21).***

Treatment acceleration (via hypofractionation), with anoverall treatment time (OTT) of less than 6–7 weeks, may improve cure rates by reducing the period for proliferation and repopulation.Even when combined into a 3-week regimen, hypofractionated and conventional fractionation exhibited equivalent long-term efficacy, cosmetic effects, and delayed hazardous consequences.As a result, hypofractionation could be utilized instead of conventional fractionated radiotherapy. An MD Anderson Cancer Center randomized study compared conventionally fractionated (50 Gy/25 fr) versus hypofractionated (42.5 Gy/16 fr) radiotherapy, physician-reported fatigue was lower for hypo-fractionation and patients reported less lack of energy and a lower incidence of issues in meeting family needs.Different hypofractionation schedules showed acceptable adverse reactions, good efficacy and aesthetic outcomes.Studies show that hypofractionated radiotherapy following breast-conserving surgery is a feasible and cost-effective choice ***(22).***

Hypofractionated whole breast irradiation has also laid the groundwork for the exploration of a hypofractionated approach in the setting of hypofractionated post-mastectomy radiation therapy. While standard fractionation, which is typically delivered over 5 to 7 weeks, is considered the standard of care in setting of post-mastectomy radiation therapy, recently published trials support the safety and efficacy of a hypofractionated approach ***(23).***

Hypofractionation has also demonstrated efficacy in postmastectomy without evidence of increased adverse effects or inferior locoregional tumour control when compared to conventional radiotherapy; in fact, because of the shorter duration, it has the added benefit of increased compliance, which can help in accommodating more breast cancer patients in a calendar year, resulting in a shorter waiting list, increased turnover and lower treatment costs.Several trials emerged to support the use of hypofractionation.

TOXICITIES OF RADIOTHERAPY

SKIN TOXICITIES

- Early Skin Toxicities

– Most breast cancer patients (about 95%) who received radiotherapy experience acute skin toxicity.Around the 2nd to 4th week of radiation treatment, acute toxicities generally start. Most of acute skin toxicities occur within 30 days from completion of therapy ***(24).***

Table (1): Comparison between different grading tool for acute skin toxicity.

Toxicity	Grade 1	2a	2b	3	4
RTOG Skin	Follicular, faint or dull erythema/epilation/dry desquamation/decrease sweating.	Tender or bright erythema ± dry desquamation.	Patchy moist desquamation; moderate edema.	Confluent; moist desquamation other than skin folds, pitting edema.	Ulceration, hemorrhage, necrosis
CTCAE (Common Terminology Criteria for Adverse Events) v4.0 Radiation Dermatitis	Faint erythema or dry desquamation.	Moderate to brisk erythema or patchy moist desquamation (2c); mostly confined to skin folds and crease; moderate edema (tenderness is graded separately in the Pain category)		Confluent moist desquamation ≥1.5cm diameter and confined to skin folds; pitting edema.	Skin necrosis or ulceration of full thickness; may including bleeding not induced by minor trauma or abrasion.

CTCAE v4.0 Skin ulceration	Combined area of ulcers<1cm; non-blanchable erythema of intact skin with associated warmth or edema.	Combined area of ulcers 1-2 cm; partial thickness skin loss involving skin or subcutaneous fat.	Combined area of ulcers >2cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia.	Any size ulcer with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures with or without full thickness skin loss.

- Late Skin Toxicity

– Late skin toxicity is defined as side effect of treatment that occurs more than 3 months following radiotherapy. Like acute toxicities, these can range from mild to sever; thus, these outcomes should be considered as important factors relative to maintaining quality of life after treatment. Late skin toxicities include radiation-induced fibrosis, atrophy, hyperpigmentation and telangiectasia ***(24).***

– **Table (2):** Comparison between different grading tool for late skin toxicity.

	Grade 1	Grade 2	Grade 3	Grade 4
RTOG/EORTC				
Skin	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss.	Marked atrophy, gross telangiectasia.	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat.	Moderate fibrosis, but asymptomatic; slight field contracture,	Severe induration and loss of subcutaneous tissue, field contracture,	Necrosis

		≤10% linear reduction.	≥10% linear reduction	
LENT/SOMA – Brest Subjective				
Pain	Occasional and minimal hyper-sensation	Intermittent and tolerable	Persistent and intense	Refractory, excruciating
LENT/SOMA – Breast Objective				
Telangectasia	<1cm^2	1-4cm^2	>4cm^2	
Fibrosis	Barely palpable, increased density	Definite increased intensity and firmness	Very marked density, retraction, and fixation	
Edema	Asymptomatic	Symptomatic	Secondary dysfunction	
Retraction, atrophy	10-25%	>25-40%	>40-75%	Whole breast
LENT/SOMA - Skin				
Pigmentationchange	Transitory, slight	Permanent, marked	-	-

RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; LENT/SOMA, late effects of normal tissue task force, SOMA, subjective, objective, management and analytic ***(25).***

– LYMPHEDEMA

Similar to nodal surgery, receiving any form of radiation to the axilla has been proven to increase a patient's risk of developing lymphedema from 10.8% to 15.5%, and the incidence among patients underwent RLNR following ALND ranges from 18.2% to 24.3%.Although the risk of developing lymphedema among patients who receive RLNR following SLNB is lower (ranging from 6.1% to 11%), it is clear that RLNR influences a patient's risk of developing lymphedema ***(26).***

– **Table (3):** International society of lymphology staging of lymphedema *(27).*

Stage	International society of lymphology
0	Latent or subclinical patients complain of heavy sensation and/or numbness in arm. May exist for months to years before overt edema occures
1	Early accumulation of protein-rich fluid. May have soft, pitting edema: limb elevation leads to complete resolution of swelling. No fibrosis
2	Limb elevation alone rarely reduces swelling Fibrosis present: reduces ability of skin to indolent with pressure
3	Lymphoblastic elephantiasis: no pitting edema present. Sever fibrosis and hypertrophic skin changes such as hyperkeratosis, fat deposits and warty outgrowths

– CARDIOTOXICITY

– Post-operative radiotherapy has been approved to be associated with cardiac toxicity and increase in deaths not-related to breast cancer. Women received radiotherapy has 4.3% increase in non-breast cancer deaths than those didn't not receive radiotherapy

– PULMONARY TOXICITY

– Radiation pneumonitis

– The radiation pneumonitis (RP) is the most common pulmonary toxicity, although total number of RP in relation to number of females received radiotherapy is quit little as usually a small radiation dose reaches to a small lung volume ***(28).***

– Pulmonary Fibrosis

Pulmonary fibrosis is considered as late lung toxicity. It is a rare event ***(29)***

– COSMETIC ASSESSMENT

– Parameters of Cosmetic Assessment

– To evaluate the cosmetic result of WBRT, an observer usually identifies and evaluates color, shape, geometry, irregularity and roughness of the visual appearance of the treated breast,

compared to the untreated one. Asymmetry is the key parameter for analyzing cosmetic results. Asymmetry in size, is probably the most important contributor to global cosmetic result. Surgery and radiotherapy derived fibrosis can also impact on symmetry without impairing the size of the breast by causing upward retraction of the inferior mammary sulcus and the nipple-areolar complex (NAC). Scar visibility and length also influences cosmetic results contributing to asymmetry ,Other aspects that need to be considered are generally attributed to radiotherapy and include differences in color, both hyperpigmentation of the treated breast, and hypopigmentation of the NAC complex and to a lesser effect, telengiectasias ***(30)***

– How Can Patients Be Evaluated

Patients are usually evaluated either by direct observation or indirectly through conventional photographs or slides, special cameras telecameras or more recently through digital images. Direct observation of patients is the most complete form of cosmetic evaluation as it allows not only for a global appreciation of results but also for other factors that are not visualized in captured images, such as skin atrophy and edema of the breast and arm . Photographs allow for the visualization of the main factors contributing to final cosmetic results such as symmetry of both breasts, scar visibility and length, and color differenced. There are also several practical advantages associated with photographs: images can be saved permanently; visualized when necessary; easily analyzed by different observers. More recently, digital photography has almost replaced paper prints and slides, making the whole process much easier and less expensive, while maintaining picture quality ***(30)***

– The most widespread scale used in published papers until today is the Harvard scale, introduced by Jay Harris in 1979. It classifies cosmetic results in four classes: excellent; good; fair; poor.

– Table (4): Harvard/NSABP/RTOG Breast Cosmesis Grading Scale.

1. Excellent	When compared to the untreated breast, there is minimal or no difference in the size or shape of treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue or fluid accumulation within the breast, but not enough to change the appearance.
2. Good	There is a slight difference in the size or shape of treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
3. Fair	Obvious difference in the size and shape of treated breast. This change involves one-quarter or less of the breast. There can be moderate

	thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
4. Poor	Marked change in the appearance of the treated breast involving more than one-quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of breast. Severe scarring and thickening of the breast, which clearly alters the appearance of breast, may be found.

– NASBP, National Surgical Adjuvant Breast and Bowel Project; RTOG, Radiation Therapy Oncology Group *(31).*

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