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Review Article

Then and Now: Non metastatic Breast cancer: A Review Literature

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Abstract

Breast cancer is most common cancer worldwide among females. It is most thoroughly studied and investigated area in the field of oncology. It is disease of predominantly young females and has well known etiological factors. The management has evolved from extensive surgery in the past to the limited surgical excision. The awareness among females has also led to earl diagnosis and prompt management. The critical area of interest now lies in the field of radiation therapy where different techniques are used to enhance the local control and improve the cosmesis. This review article focuses on general outline of the anatomy, clinical features, diagnosis and management focusing on the evolution of the radiotherapy techniques especially in early stage breast cancer.

Keywords: breast cancer; non- metastatic; breast conserving therapy; radiotherapy; brachytherapy boost; cosmetic outcome

Introduction

The term "Cancer" is derived from the Greek word "*Karkinos"* (for crab) which refers to a generic non-communicable disease (NCD) characterized by growth of malignant (cancerous or neo-plasms) abnormal cells (tumor/ lump) in any part of the human body. In spite of good advancements for diagnosis and treatment, cancer is still a big threat to our society.

The female breast lies on the anterior chest wall superficial to the pectoralis major muscle. The breast extends from the midline to near the mid-axillary line and cranial caudally from the second anterior rib to the sixth anterior rib. The upper outer quadrant of the breast extends into the region of the low axilla and is frequently referred to as the axillary tail of Spence. This anatomical feature results in the upper outer quadrant of the breast containing a greater percentage of total breast tissue compared with the other quadrants, and, therefore, a greater percentage of breast cancers occur in this anatomical location. The breast parenchyma is intermixed with connective tissue, which has a rich vascular and lymphatic network.

Extent

(i) Vertically, it extends from the second to the sixth rib.

(ii) Horizontally, it extends from the lateral border of the sternum to the mid-axillary line.

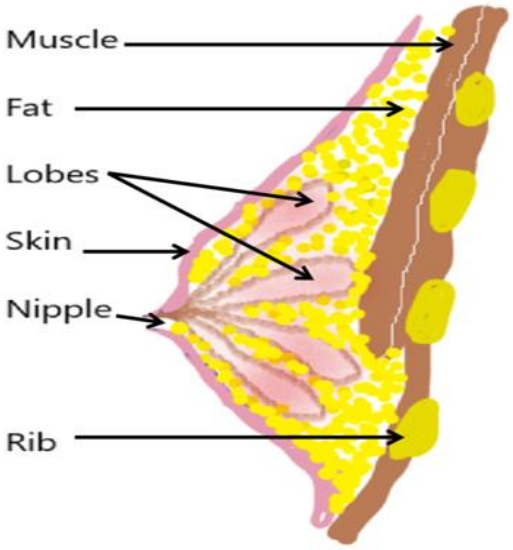

Figure 1: Coronal section of the breast and the inner structure

The predominant lymphatic drainage of the breast is to axillary lymph nodes, which is commonly described in three levels, based on the relation of the lymph node regions to the pectoralis minor muscle.

Lymph node level	Anatomic relation
Level I	Caudal and lateral to the pectoralis minor muscle
Level II	Below the pectoralis minor muscle
Level III	Cranial and medial to the pectoralis minor muscle

Table 1: Lymph nodal levels of breast and its relation to the anatomical structures

Other group of lymph nodes involved are-

- Supraclavicular lymph nodes
- Internal mammary group of lymph nodes

Epidemiology

Cancer of the breast is one of the most common cancers among women worldwide. In 2018, this was about 11.6% of the total cancer cases in both sexes. In India, breast cancer is now most common cancer and accounts for 14% of all cancer cases. It has been estimated that in 2018, worldwide there were 2088849 cases of breast cancer, and 626679 deaths due to breast cancer. A large proportion of the global burden occurs in the developed countries where it accounts for almost 24.2% of all female cancers. Although breast cancer incidence is high in developed countries compared to India, the mortality rate in India is high (6.6% vs 12.1%)[1]. India continues to have a low survival rate for breast cancer, with only 66.1% women diagnosed with the disease between 2010 and 2014 surviving, a Lancet study found. According to estimates, at least 17,97,900 women in India may have breast cancer by 2020 [2]. India is the largest country among all countries of Southern Asia. It has a population of 432.20 million women aged 15 years and older who are at risk of developing breast cancer. Current estimates of GLOBOCAN 2018 indicate that every year in India 162468 women are diagnosed with breast cancer and 87090 die from the disease. Breast cancer in India varies from as low as 5 per 100,000 female population per year in rural areas to 30 per 100,000 female population per year in urban areas [3].

Indian cities	Breast cancer percentage	Crude rate per 100000	Age adjusted rank per 100000
Mumbai	28.8	33.6	33.6
Bangalore	27.2	29.3	34.4
Chennai	30.7	40.6	37.9
Thiruvananthapuram	28.5	43.9	33.7
Dibrugarh	19	12.7	13.9
New Delhi	28.6	34.8	41
Barshi rural	20	13.2	12.4

Table 2: Ranking and rates for breast cancer (NCRP 2012)

Clinical Presentation

The majority of patients with T1 or T2 breast cancers presents with a painless or slightly tender breast mass or have an abnormal screening mammogram. Patients with more advanced tumors may have breast tenderness, skin changes, bloody nipple discharge, or occasionally change in the shape and size of the breast. Rarely, patients may present with axillary lymphadenopathy or even distant metastasis. The duration of clinical symptoms may vary from weeks to years. Olivotto *et al.*,found that delays in diagnosis of 6 to 12 months led to an increased tumor size and more lymph node metastases compared with patients diagnosed within 2 to 4 weeks of an abnormal screening mammogram[4].

Age incidence rates in India suggest that the disease peaks at a younger age (eg, 40-50 years) than in Western countries and as a result, the majority of new diagnoses occur in pre-menopausal women. Raina *et al*, found the mean age at diagnosis was 47 years and 49.7% were premenopausal, 96% presented with lump[5]. Most advanced primary

tumors are associated with axillary lymph node involvement. Local disease progression can lead to ulceration of skin, pain, bleeding infection. Progression of untreated regional lymphatic disease can cause pain, brachial plexopathy, arm edema, obstruction and thrombosis of brachial vasculature and skin ulceration.

Clinical evaluation and Diagnostic work- up

- Histopathological examination: FNAC or Core biopsies to establish invasive cancer.
- Imaging including: mammography, ultrasonography (USG) examination, CT Scan, PET and Magnetic Resonance Imaging (MRI), Bone scan
- Laboratory examination: CBC, Blood chemistry, Urinalysis
- Others: Hormone receptor status, Genetic analysis

Risk factors

Includes age, early menarche, late menopause, prolonged use of HRT, family history, lower parity, BRCA1 or 2 mutation[6]. MacMahaon *et al.*, demonstrated a nearly linear relationship between relative risk of breast cancer and age at first child birth with women age 20 to 25 having nearly 50%reduction in relative risk compared to nulliparous women. They also demonstrated that in comparison to women having menopause between 45 to 54 (relative risk 1), women with menopause before 45 have a relative risk of 0.73% and women with menopause after 54 have a relative risk of 1.48[7].

Women with a second degree relative with breast cancer have risk of 1.5 and for women with first degree relative the risk is about 1.7 to 2.5. Between 20 to 25% of women diagnosed with breast cancer have a positive family history and approximately 10% have an autosomal dominant pattern of inheritance[8]. A pooled analysis of prospective studies by Van den *et al* in 2000 demonstrated risk of breast cancer to be 30% higher in post menopausal women with BMI over 31 compared to women with BMI of 20.The higher risk with increased BMI in post menopausal women is likely due to higher estradiol levels associated with increased adipose tissue and aromatase activity, involved in conversion of androgen to estradiol [9]. Other important risk factors being personal history of breast cancer, radiation exposure to chest wall alcohol consumption, increased mammographic density.

Screening

Breast cancer screening guidelines are given by-

- American college of radiology
- American college of surgeons
- National cancer institute

Age group	**ACS (2003) GUIDELINE**
20-39 yr	BSE optional; CBE every 3 years.
40-49 yr	Annual mammography and CBE from 40 years.
>49yr	Annual mammography and CBE as long as a woman is in reasonably good health.
Age group	**NCI (2002) GUIDELINE**
20-39 yr	No recommendation
40-49 yr	Mammography every 1–2 years
>49yr	Mammography every 1–2 years

1. Physical Examination

Preoperative assessment of tumor size is commonly estimated by inspection and palpation. The accuracy of clinical assessment is influenced by patient and observer factors and is not useful for clinically occult tumors and is prone to overestimating actual tumor size[10]. Clinical examination has been found to have low sensitivity and specificity (36% and 39% respectively) in the evaluation of axillary lymph nodes. It cannot assess the number of nodes, nodes in depth and nodes of small size. Also it cannot distinguish between reactive and malignant nodes or detect extra capsular extension [11]. Physical examination alone has long been recognized as inaccurate in predicting axillary metastases, and is associated with false negative and false positive rates of 25% to 38%. Internal mammary group of lymph nodes are clinically not evaluable [12].

2. Mammography

Mammograms are by far the most common breast cancer screening tool and bilateral mammograms should be performed routinely in the work-up of the breast cancer patient. Mammography uses low energy x-rays to examine the compressed breast. Contrast in mammography results from differences in the absorption or attenuation of x-rays by different tissues in the breast. This technique has been in use for about 40 years and is the current gold standard for diagnosing breast disease. In mammography, lymph nodes are visible on standard projections, and it is possible to differentiate between normal and pathological nodes. Normal nodes are moderately attenuated, the fatty hilus being seen as a low attenuated part. Normal nodes can vary in size from a few millimeters to several centimeters. Pathological nodes are of greater density than normal nodes and the hilum disappears. The form also becomes more expanded from oval to round but the size is not necessarily increased. However, in the standard projections, only part of axilla can be seen, and during exposure of the mammogram, pathological nodes can be pushed outside the mammographic image. Mammography is therefore not a reliable method in axillary lymph node imaging. The Breast Imaging Reporting and Data Systems (BI-RADS) classification system, outlined below has been widely adopted in classifying mammograms with respect to appropriate follow-up and/or intervention [13].

Category 1 Negative	There is nothing to comment on. The breasts are symmetric and no masses, architectural disturbances, or suspect calcifications are present.
Category 2 Benign finding	This is also a negative mammogram, but the interpreter may wish to describe a finding. Involuting, calcified fibroadenomas, multiple secretory calcifications, fat-containing lesions such as oil cysts, lipomas,

	galactoceles, and mixed-density hamartomas all have characteristic appearances, and may be labeled with confidence. The interpreter might wish to describe intramammary lymph nodes, implants, and the like, while still concluding that there is no mammographic evidence of malignancy.
Category 3 Probably benign finding short-interval follow-up suggested	A finding placed in this category should have a very high probability of being benign. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability. Data are becoming available that shed light on the efficacy of short-interval follow-up. At present, most approaches are intuitive. These will likely undergo future modification as more data accrue as to the validity of an approach, the interval required, and the type of findings that should be followed.
Category 4 Suspicious abnormality biopsy should be considered	These are lesions that do not have the characteristic morphologies of breast cancer but have a definite probability of being malignant. The radiologist has sufficient concern to urge a biopsy. If possible, the relevant probabilities should be cited so that the patient and her physician can make the decision on the ultimate course of action.
Category 5 Highly suggestive of malignancy appropriate action should be taken	These lesions have a high probability of being cancer.
Category 0 Need additional imaging evaluation	Finding for which additional imaging evaluation is needed. This is almost always used in a screening situation and should rarely be used after a full imaging workup. A recommendation for additional imaging evaluation includes the use of spot compression, magnification, special mammographic views, ultrasound, and so forth.

Table 3: American College of Radiology Breast Imaging Reporting and Data Systems (BI-RADS) Assessment Categorize Mammography

3. Ultrasound

Ultrasound, also called sonography, uses high frequency sound waves to penetrate breast tissue and measures the reflection from different tissues in the breast. Due to inability to consistently detect early signs of cancer such as microcalcifications, ultrasound is not routinely used for breast cancer screening but primarily to distinguish solid tumors from fluid filled cysts, evaluate suspected carcinomas in mammographically dense breasts and for biopsy guidance[14]. Sonography is an important adjunct to mammography to identify, characterize, and localize breast lesions, and it has the added advantage of not being limited by dense breasts. It also has no radiation or compression. Consequently, sonography is more effective for women younger than 35 years of age[15]. Breast ultrasound examinations can obtain any sectional image of breast, and observe the breast tissues in real-time and dynamically. Ultrasound imaging can depict small, early-stage malignancies of dense breasts, which is difficult for mammography to achieve.

4. Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is emerging as a promising tool for screening breast cancer especially among high risk women. MRI has also demonstrated greater sensitivity in detecting small (less than 1 cm) lesions and succeeds in certain scenarios where other imaging modalities are challenged, such as imaging dense breasts, the post-operative breast and augmented breasts. In a review of MRI in the management of breast cancer, Hylton summarized the potential for the current use of MRI: to complement mammography in screening, for differential diagnosis of questionable findings on physical examination, mammography, and ultrasound; and assessment of response in the Neoadjuvant treatment of breast cancers[16]. The American Society of Breast Surgeons has outlined indications for the use of breast MRI. These include axillary nodal metastasis with unknown primary, determination of ipsilateral or contralateral disease in newly diagnosed breast cancer patients with invasive lobular cancer, difficult mammographic assessments, monitoring response to Neoadjuvant therapy, screening of high-risk patients, and evaluation of suspicious clinical findings or imaging studies with indeterminate work-ups. Drawbacks of MRI include moderate diagnostic specificity, false-positive findings requiring additional biopsies, patient distress, prolongation of the pre surgical work-up and the potential for overestimation of tumor size and higher cost[17].

Breast Cancer Diagnosis

Histopathological or cytological examination is the only definitive way to determine whether a mass is malignant or benign. As such, abnormalities detected with any of the afore-discussed techniques might be queried by biopsy. Common forms of breast biopsy include fine needle aspiration (FNA), core biopsy, vacuum assisted biopsy and open surgical biopsy. Breast biopsy of any suspicious mass is mandatory. The biopsy usually can be done using local anesthesia; the patient should be informed of the nature of the lesion to allow for her greater participation in therapeutic decisions. There has been no evidence that delay in treatment up to 2 weeks after biopsy worsens prognosis[18].

Prognostic factors in breast cancer

In patients of carcinoma breast undergoing single or multimodality treatment, outcome of treatment depends on various prognostic factors present before treatment.

The prognostic factors are

1. Tumor size
2. Axillary nodal status
3. Tumor type
4. Tumor grade
5. Hormonal receptors
6. Micrometastsis
7. Lymphatic and vascular invasion
8. Age
9. Tumor location
10. Race
11. Obesity and BMI
12. Pregnancy
13. Smoking

Stage at diagnosis is the best predictor of prognosis. Early stage breast cancer is curable in most patients by surgery +/- radiotherapy, with 5-year survival of 95%. Size of tumor is another prognostic factor in carcinoma breast. According to Carter *et al.*, survival rates varied from 45.5% for tumor diameters equal to or greater than 5 cm with positive axillary nodes to 96.3% for tumors less than 2 cm and with no involved nodes. The relation between tumor size and lymph node status was investigated in detail. Tumor diameter and lymph node status were found

to act as independent but additive prognostic indicators. As tumor size increased, survival decreased regardless of lymph node status; and as lymph node involvement increased, survival status also decreased regardless of tumor size. A linear relation was found between tumor diameter and the percent of cases with positive lymph node involvement[19].

Rosen *et al.*, found a close correlation between tumor size and recurrence free survival[20].

Tumor size	Recurrence free survival
<1cm	88%
1.1 to 3cm	72%
3.1 to 5cm	59%

Table 4: Corelation of tumor size and recurrence free survival according to Rosen et al.

According to the number of axillary lymph nodes involved, patients are grouped into four prognostic categories

- Node negative
- 1 – 3 nodes involved
- 4 – 9 nodes involved
- >/= 10 nodes involved

Although up to 30% to 40% of T1 or T2 clinically node-negative breast cancers may have pathologically involved lymph nodes, data from NSABP-04 suggest that less than half of clinically negative but pathologically positive axilla will experience a clinical relapse in the axilla.

Tumor Location	Axillary lymph node status	Rate of involvement of axillary lymph node
Medial/ central	0 + ALN	6% (27/428)
	1-3 + ALN	26% (41/160)
	4-6 + ALN	43% (21/49)
	≥7 + ALN	40% (44/110)
Lateral	0 + ALN	3% (12/456)
	1-3 + ALN	14% (34/238)
	4-6 + ALN	20% (18/90)
	≥7 + ALN	43% (63/148)

Management of Breast Cancer

Breast cancer is now considered to be a systemic disease from the outset, with most patients with early breast cancer developing metastases whatever the treatment undertaken. The need for and selection of therapy is based on a number of prognostic & predictive factors. They include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, tumor HER2 receptor, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age and menopausal status. Breast cancer therapy comprises local treatments and systemic treatments and often a combination of both. Local treatments include surgery and radiation. The aim of local treatments is to eradicate the disease at source or the primary tumor. Systemic treatments such as chemotherapy and hormone therapy are generally directed against the metastasis as well as locally.

Chemotherapy in non-metastatic breast cancer:

Even following effective local treatment, many patients develop metastasis over time and improvements in local control have been shown to provide, at best, only a small decrease in distant metastasis[18,21]. This was thought to be because of the concept of micrometastasis at the time of initial presentation. This led to the generation of the concept of systemic therapy for accomplishing long term improvement in the outlook of the disease.

The NSABP (National Surgical Adjuvant Breast & Bowel Project) evaluated the effect of adding cyclophosphamide to methotrexate and 5 fluorouracil (CMF) in the B-19 study. Estrogen negative (ER) negative patients underwent 6 months of treatment with either CMF or MF after surgery. Disease free survival (DFS) rates were statistically significantly higher for those taking CMF (82 vs 73%, $p < 0.001$)[22]. The Milan study which evaluated the effect of 1 year of adjuvant CMF vs no chemotherapy in women with node-positive disease demonstrated a significant reduction in recurrence among those who received chemotherapy. After 20 years of follow-up, the number of women alive and free from recurrence was still significantly higher than it was among those receiving no chemotherapy, 36 % vs 27% respectively[23]. The current available data indicate that effective regimens for node-positive patients include six cycles of 5-fluorouracil, adriamycin and cyclophosphamide (FAC) or 5-fluorouracil, epirubicin and cyclophosphamide (FEC), or four cycles of FAC or FEC or AC followed by four cycles of a taxane, or six cycles of taxane, adriamycin and cyclophosphamide (TAC). For node-negative patients, four cycles of AC, six cycles of FAC or FEC, and six cycles of CMF are reasonable options.

	C9344 (Henderson C *et al* , 2003)[24]	B28 (Mamounas EP *et al*, 2003)[25]	C9741 (Nabholtz JM *et al*, 2002)[26]	BCIRG 001 (Nabholtz JM *et al*, 2001)[27]
N	3170	3060	2005	1491
Median follow-up	69 months	65 months	36 months	33 months
Superior Arm	AC --> P	AC --> P	AC --> P or A --> P --> C every 2 weeks	DAC
DFS Hazard Ratio	0.83 (p = .0098)	0.83 (P = 0.008)	0.74 (P = .01)	0.68 (P = .0002)
Death Hazard Ratio	0.82 (p = .0098)	NS	0.69 (P = .013)	0.76 (P = .049)

Table 5: Comparison of Breast Cancer Trials Evaluating Taxanes

Hormonal therapy in non metastatic breast cancer:

Estrogen, a hormone produced by the ovaries, promotes the growth of many breast cancers. Women whose breast cancers test positive for estrogen receptors can be given hormone therapy to block the effects of estrogen on the growth of breast cancer cells. Tamoxifen, the most common antiestrogen drug, is effective in both postmenopausal and premenopausal patients whose cancers are positive for hormone receptors. Recurrence and survival benefits generally increase with longer duration of tamoxifen use and have been shown to persist for at least 10 years following treatment[28].

Preliminary results of the ATLAS (Adjuvant Tamoxifen, Longer Against Shorter) International randomized trial of 10 versus 5 years of adjuvant tamoxifen among 11500 women showed that continuation of tamoxifen beyond the first 5 years reduces recurrence over the next few years, but further follow-up is needed to assess reliably the longer-term effects on recurrence and the net effects, if any, on mortality[29].

More recently, Trastuzumab has been shown to be effective in early-stage breast cancer that overexpresses HER2. The combined results of two large trials indicate that adding Trastuzumab to standard chemotherapy for early-stage HER2 positive breast cancer reduced the risk of recurrence and death by 52% and 33%, respectively, compared to chemotherapy alone[30]. In 2006, the FDA approved Trastuzumab for all HER2 positive breast cancers. All invasive breast cancers should be tested for the HER2 protein in order to identify women who would benefit from this therapy.

Surgery:

The primary goal of breast cancer surgery is to remove the tumor from the breast and to assess the stage of disease. The various surgical options are:

Lumpectomy - In lumpectomy, only cancerous tissue plus a rim of normal tissue is removed.

Simple/Total mastectomy - includes removal of the entire breast.

Radical mastectomy- Radical mastectomy is rarely used due to the proven effectiveness of less aggressive and disfiguring surgeries.

Modified radical mastectomy- This includes removal of the entire breast and lymph nodes under the arm, but does not include removal of the underlying chest wall muscle, as with a radical mastectomy.

Breast conserving therapy in early stage breast cancer cases

Breast conserving therapy include

- Wide local excision with clear margins
- Axillary lymph node dissection
- Irradiation to whole breast with tumor bed boost or partial breast irradiation

The earliest prospective trial by Atkins *et al* in 1972 comparing breast conservation with radical mastectomy which included 370 women with stage I and II breast cancer showed no survival benefit for stage I disease, in stage II the recurrence rates and distant metastasis were higher in the group treated with local excision followed by irradiation. The EORTC Breast Cancer Cooperative Group comparing radical mastectomy with breast conservation showed actuarial 8 years local control was similar in both arms. The U.S. National Cancer Institute reported results of randomised study in T1-2/N0/M0 breast cancer treated with modified radical mastectomy or breast conservation, there was no difference with regard to overall survival, with median follow up of 18.4 years. In1971, the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the B-04 study, a randomized clinical trial conducted to resolve controversy over the surgical management of breast cancer. The 25-year findings from that study showed that there was no significant difference in survival between women treated with the Halsted radical mastectomy and those treated with less extensive surgery[12]. NSABPB-06 TRIAL evaluated the efficacy of breast-conserving surgery in women with stage I or II breast tumors that were 4 cm or less in diameter. The outcome for women who were treated with lumpectomy alone or with lumpectomy and postoperative breast irradiation was compared with that for similar women who were treated with total mastectomy. There was no significant differences in survival among the women in the three treatment groups and demonstrated a significant decrease in the rate of recurrent cancer in the ipsilateral breast after lumpectomy plus irradiation[31]. Bartelink *et al.*, studied the long-term impact of a boost radiation dose on local control, fibrosis, and overall survival for patients with stage I and II breast cancer who underwent breast conserving therapy. They concluded that After a median follow-up period of 10.8 years, a boost dose of 16 Gy led to improved local control in all age groups, but no difference in survival at 10 years, the cumulative incidence of local recurrence was 10.2% versus 6.2% for the no boost and the boost group, respectively ($P < .0001$). Severe fibrosis was statistically significantly increased ($P <.0001$) in the boost group, with a 10-year rate of 4.4% versus 1.6% in the no boost group ($P<.0001$). Survival at 10 years was 82% in both arms[32,33]. The meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed the need for radiotherapy after tumorectomy by showing that breast irradiation reduced the 5-year local recurrence rate from 26% to 7%.

The UK Standardisation of Breast Radiotherapy (START) Trial A randomized 2236 women with early breast cancer (pT1-3a pN0-1 M0) between 1998 and 2002, to receive 50 Gy in 25 fractions of 2.0 Gy versus 41.6 Gy or 39 Gy in 13 fractions of 3.2 Gy or 3.0 Gy over 5 weeks after primary surgery. After a median follow up of 5.1 years the rate of local-regional tumor relapse at 5 years was 3.6% after 50 Gy, 3.5% after 41.6 Gy, and 5.2% after 39 Gy. The estimated absolute differences in 5-year local-regional relapse rates compared with 50 Gy were 0.2% after 41.6 Gy and 0.9% after 39 Gy[34]. This result is consistent with that of the START Trial B, in which 40 Gy in 15 fractions over 3 weeks seemed at least as safe and effective as 50 Gy in 25 fractions. The combined trials present mounting evidence that hypofractionation is a safe and effective approach to breast cancer radiotherapy[35].

	Institut Gustave-Roussy (1972–84)	Milan (1973–80)	NSABP B-06 (1976–84)	NCI (1979–87)	EORTC (1980–86)	Danish (1983–89)
Number of patients	179	701	1219	237	874	904
Stage	1	1	1 and 2	1 and 2	1 and 2	1,2,3
Surgery	Excision	Quadranectomy	Lumpectomy	Excision	excision	excision
Overall survival (%) CS+ RT vs mastectomy	73 vs 63	42 vs 41	46 vs 47	59 vs 58	65 vs 66	79 vs 82
Local recurrence (%) CS+ RT vs mastectomy	9 vs 14	9 vs 2	14 vs 10	22 vs 6	20 vs 12	3 vs 4

Table 6: Prospective randomized trials comparing conservative surgery and radiation with mastectomy for early stage breast cancer

Brachytherapy

Brachytherapy is a type of radiation therapy that utilizes natural radioactive isotopes or radio-nucleotides that are temporarily or permanently implanted in or near the tumor or target tissue to treat malignancies or certain benign conditions. Brachytherapy is based upon the principle that the dose decreases rapidly with distance from source of radiation. Therefore, brachytherapy allows the delivery of a high dose of radiation to well defined target while the dose of radiation of adjacent normal structure is relatively low.

The brachytherapy dose rate is determined by the intensity of the radioactive source. Brachytherapy dose rate is described as low dose rate (LDR), high dose rate (HDR) and pulse dose rate (PDR).

LDR:

In a temporary LDR implant, the radiation dose is delivered continuously over several days in a hospital setting, with patient managed under radiation safety precautions with limits to nursing and visitor time in order to protect them from low level radiation exposure.

HDR:

Performed by using a remote after loading device to transport the radioactive source to the target. HDR allows the dose to be delivered in minutes. It is often given in a series of multiple fractions and can be performed either on an outpatient or inpatient basis.

PDR:

Uses sources of intermediate strength and delivers a series of doses on a 1-2 hourly schedule over 1-2 day treatment period. It is also form of HDR remote after loading.

Brachytherapy is further described by the means the radioactive material is placed in to the tumor / target tissue. Interstitial application- sources are directly inserted in to tumor / target tissue. Intracavitary application-sources are inserted into a body cavity. Surface application-sources are placed directly on an external tumor/target surface.

LDR Brachytherapy

Low-dose-rate (LDR) brachytherapy has traditionally been used for treating prostate, head and neck, breast, cervical, and endometrial cancers as well as obstructive bile duct, esophageal, or bronchial lesions (Devlin PM. Brachytherapy Applications and Techniques). It has been practiced for over a century with a variety of sources including radium-226, cesium-137, and more recently iridium-192, iodine- 125 and palladium-103.

Low-dose-rate (LDR) brachytherapy can be given as interstitial, intra-cavitary, and intraluminal to a wide variety of treatment sites. Lowdose-rate brachytherapy is accomplished by temporary implants, in which radioactive sources are ‘‘after loaded’’ for a period of a few hours or days into applicators that are placed temporarily into the patient or permanent implants, in which the radioactive sources are permanently inserted into the cancerous tissue.

Source handling and loading into the applicator or tissue can be performed manually or remotely, with source loading performed by a computerized unit. Lowdose- rate brachytherapy is delivered at dose rates of 40-200 cGy per hour at a designated point. Remote after loading pulse-dose-rate (PDR) brachytherapy is a method that is delivered over a protracted time in periodic (usually hourly) pulses at rates similar to those used for LDR brachytherapy.

Advantages of LDR brachytherapy

LDR offers many advantages, first and foremost being the availability of data of more than 100 years. Besides it has standard doses and standardized treatment plans. The need of changing source (depending on isotope used) is lesser and less shielding is needed during the treatment.

Disadvantages of LDR brachytherapy-

LDR has its own associated disadvantages. Often inpatient treatment requires prolonged bed rest. Radiation exposure to staff is more. Use is limited by available source strength. Many of the LDR sources are no longer being manufactured. Computer-based dose optimization, advances in radiation safety, and improved nursing care are important reasons why LDR brachytherapy is being supplanted by HDR brachytherapy (Inoue T *et al.,* 1996)

Advantages of HDR brachytherapy-

- DR eliminates radiation exposure hazard for care givers and visitors. It also eliminates source preparation and transportation. Since there is only one source, there is minimal risk of losing radioactive source.
- Allows shorter treatment time: There is less patient discomfort since prolonged bed rest is eliminated. It is possible to treat patients who may not tolerate long periods of isolation and those who are at high risk for pulmonary embolism due to prolonged bed rest. There is less risk of applicator movement during therapy. It also reduces hospitalization costs since outpatient therapy is possible. HDR may allow greater displacement of nearby normal tissues (by packing or retraction) which could potentially reduce morbidity. It is possible to treat a larger number of patients in institutions that have a high volume of brachytherapy patients but insufficient inpatient facilities (e.g., in some developing countries). Besides it also allows intraoperative treatments, which are completed while patient is still in the operating room.
- HDR sources are of smaller diameter than the Cesium sources that are used for intracavitary LDR: This reduces the need for dilatation of the cervix and therefore reduces the need for heavy sedation or general anesthesia. Thus high-risk patients who are unable to tolerate general anesthesia can be more safely treated. Smaller size allows for interstitial, intraluminal and percutaneous insertion.

- HDR makes treatment dose distribution optimization possible: Variations of the dwell times of a single stepping source allow a almost infinite variation of the effective source strengths, and the source positions allows for greater control of the dose distribution and potentially less morbidity. Radiation Protection: H

Disadvantages of HDR brachytherapy-

- Radiobiological: The short treatment times do not allow for the repair of sublethal damage in normal tissue or the redistribution of cells within the cell cycle or reoxygenation of the tumor cells; hence, multiple treatments are required.
- 2. Limited experience: Use of HDR has only limited experience at most of the centers. Only a few centers in the United States have long-term (greater than 20 years) experience. Until recently, standardized treatment guidelines were not available; however, the American Brachytherapy Society (ABS) has recently provided guidelines for HDR at various sites (10-18).
- 3. The economic disadvantage: The use of HDR brachytherapy as compared to manual after loading techniques requires a large initial capital expenditure since the remote after loaders cost about $300,000.There are additional costs for a shielded room and personnel costs are higher as the procedures are more labor intensive.
- 4. Greater potential risks: Since a high activity source is used, there is greater potential harm if the machine malfunctions or if there is a calculation error. The short treatment times, compared to LDR, allow much less time to detect and correct error.

Boost to tumor bed after conservative therapy

There are different techniques employed for providing effective dose to tumor bed taking into account nearby normal organs constraints.

- Boost by external beam photon therapy
- Boost by proton therapy
- Boost by electron therapy
- Boost by interstitial brachytherapy

Standard breast conserving therapy(BCT) involves quadrantectomy, axillary sampling, radiation of the residual breast tissue (with / without regional nodal irradiation) and addition of appropriate systemic therapy where needed. The main role of radiation in BCT is in the prevention of local recurrence without affecting cosmetic outcome. Conventionally Radiotherapy (RT) in BCT includes external beam radiotherapy (EBRT) of 50Gy to the whole breast usually delivered with tangential beams in standard fraction size of 2 Gy. A supplementary tumor bed boost dose of 15 Gy – 20 Gy either with electrons or photons or an interstitial implant is added to decrease the rate of local recurrence[36].

National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the B-04 study, showed that there was no significant difference in survival between women treated with the Halsted radical mastectomy and those treated with less extensive surgery. In 1973, NSABPB-06 trial evaluated the efficacy of breast-conserving surgery in women with stage I or II breast tumors that were 4 cm or less in diameter. Patients were treated with lumpectomy. The outcome for women who were treated with lumpectomy alone or with lumpectomy and postoperative breast irradiation was compared with that for similar women who were treated with total mastectomy. After 20 years of follow-up, they found no significant difference in overall survival among women who underwent mastectomy and those who underwent lumpectomy with or without postoperative breast irradiation. The cumulative incidence of a recurrence in the ipsilateral breast 20 years after surgery was 14.3 percent among the women who underwent irradiation after lumpectomy and 39.2 percent among those who underwent lumpectomy without irradiation ($P<0.001$)[31].

Electron beam is presently the most widely used modality for delivering additional dose to the lumpectomy cavity. Treatment with electrons provides a method of shallow dose delivery with a well-localized dose distribution. In the vast majority of patients, boosting with an electron beam provides acceptable dose coverage and limited toxicity. However, there are patients for whom electrons may be less appropriate. These include patients with large breasts and deep tumors in which electron boosting may result in excessive skin dose or even increased dose to the underlying lung.

Ulutin, H. C. *et al*., (2003) published the results of 174 patients treated with brachytherapy boost after conservative surgery for early breast cancer with high risk features. Microscopic margin involvement, extensive carcinoma *in situ*, and vascular/lymphatic invasion were the main risk factors for local recurrence. Whole-breast irradiation (40 Gy in 15 fractions over 3 weeks) followed with a brachytherapy boost (Ir192 wire implant or PDR Ir192) of 25 Gy was applied. Median follow-up was 80 months. The actuarial 6-year overall survival rate was 91% and the within breast recurrence-free survival was 88%. The most common risk factor among those recurring within the breast was involved surgical margins (13 out of 17). Cosmesis was reported to be good or excellent in 79% of cases. They concluded that patients with high risk for local recurrence, tumor-bed boost with brachytherapy can provide satisfactory local control after limited surgery and external radiotherapy[37].

Vicini *et al.,* (1997) conducted institution based study with interstitial implant boosts to determine long-term impact on local control and cosmetic results. 400 cases of Stage I and II breast cancer managed with breast-conserving therapy (BCT) received Radiation consisted of 45-50 Gy external beam irradiation to the whole breast followed by a boost to the tumor bed to at least 60 Gy using either electrons ,photon or an interstitial implant. Long term local control and cosmetic outcome were assessed and contrasted between patients boosted with either interstitial implants, electrons, or photons. With a median follow-up of 81 months, there was no statistically significant differences in local recurrence rate using either electrons, photons, or an interstitial implant. Greater than 90% of patients obtained a good or excellent cosmetic result, and no statistically significant differences in cosmetic outcome were seen whether electrons, photons, or implants were used[38].

Terheyden *et al.,* (2016) compared the dosimetric data of local tumor's bed dose escalation (boost) with photon beams (external beam radiation therapy – EBRT) versus high-dose-rate interstitial brachytherapy (HDR-BT) after breast-conserving treatment in women with early-stage breast cancer. They analyzed the treatment planning data of 136 patients who received adjuvant whole breast irradiation (WBI; 50.4 Gy) and boost (HDR-BT: 10 Gy in one fraction; EBRT: 10 Gy in five fractions). Organs at risk (OAR; heart, ipsilateral lung, skin, most exposed rib segment) were delineated. They concluded that there was no difference for left-sided cancers regarding the maximum dose to the heart (HDR-BT 29.8% vs. EBRT 29.95%, $p = 0.34$). The maximum doses to the other OAR were significantly lower for HDR-BT. In the case of right-sided breast irradiation, dose of the heart 6.00% vs. 16.75% ($p < 0.01$). Compared to EBRT, local dose escalation with HDR-BT presented a significant dose reduction to the investigated OAR. Only left-sided irradiation showed no difference regarding the maximum dose to the heart. Therefore, from a dosimetric point of view, an interstitial boost complementary to WBI via EBRT seems to be more advantageous in the adjuvant radiotherapy of breast cancer[39].

Study	Electron beam %	Brachytherapy %
Fourquet *et al*., (1995)[40]	75	71
Mansfield *et al*., (1995)	95	91
Olivotto *et al*., (1989)	100	60
Perez *et al*., (1996)[41]	81	75
Ray and Fish (1983)[42]	91	52
Vicini *et al*., (1997)[43]	90	88
Roy et al (2013)[44]	80	50

Table 7: Comparison of excellent/ good cosmetic results in BCT

Manning *et al*., evaluated the feasibility, potential toxicity, and cosmetic outcome of fractionated interstitial high dose rate (HDR) brachytherapy boost for the management of patients with breast cancer at increased risk for local recurrence From 1994 to 1996, 18 women with early stage breast cancer underwent conventionally fractionated whole breast radiotherapy (50 –50.4 Gy) followed by interstitial HDR brachytherapy boost 15 Gy delivered in 6 fractions of 2.5 Gy over 3 days. They concluded that the fractionation scheme of 15 Gy in 6 fractions over 3 days is well tolerated. The volume of tissue removed from the breast at lumpectomy appears to dominate cosmetic outcome in this group of patients[45].

Poor	Marked distortion of nipple, breast asymmetry, edema, fibrosis, severe hyperpigmentation
Fair	Moderate distortion of nipple, breast asymmetry, moderate hyperpigmentation, prominent skin retraction or telangiectasia
Good	Slight distortion of nipple, skin, any visible telangiectasia, mild hyperpigmentation, absent nipple-areolar complex
Excellent	Perfect symmetry, no visible distortion

Table 8: Cosmetic outcome assessment (Manning *et al*.)[45]

	Grade 0	**Grade 1**	**Grade 2**	**Grade3**	**Grade 4**
Subjective					
Pain	None	Occasional hypersensation, pruritis	Intermittent	Persistent	Refractory
Objective					
Hyperpigmentation	None	Mild	Moderate	Severe	Nil
Fibrosis	None	<3cm	3–6 cm	>6cm	Whole breast
Telangiectasia	None	<9cm2	9–36 cm2	>36cm2	Whole field

Table 9: Late toxicity criteria (Manning *et al*.)

Cosmesis grading scale used in different studies

Pezner *et al*., employed scales to evaluate the cosmetic outcome of breast-preserving conservative treatment of patients with Stage I and II breast cancer. Two observe based cosmesis scales employed by volunteers to evaluate photographs of treated for breast cancer[46].

SCALE A	SCALE B
0 = Treated breast nearly identical to untreated breast 1 = Treated breast slightly different from untreated breast 2 = Treated breast clearly different from untreated breast, but not seriously distorted 3 = Treated breast seriously distorted	0 = Appearance of treated breast almost identical in size and configuration to opposite breast; no breast deformity from fibrosis or biopsy; no skin changes 1 = Retraction and/or skin changes involving less than ‘14 of breast 2 = Retraction and/or skin changes involving L/4 to l/2 of breast 3 = Deformity involving over % of breast

Toxicity criteria and grading

Grade 1	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)
Grade 2	Moderate induration, able to slide skin, unable to pinch skin, limiting instrumental ADL
Grade 3	Severe induration, unable to slide or pinch skin, limiting self care ADL
Grade 4	Generalized , associated with signs and symptoms of impaired breathing or feeding
Grade 5	Death

RTOG grading for acute and late skin and subcutaneous toxicities

Table 10: Skin induration grading according to NCI CTCAEv4.0[47]

Grade 0	Nil
Grade 1	Erythema
Grade 2	Early desquamation/pigmentation
Grade 3	Moderate dry desquamation /early moist desquamation
Grade 4	Blister formation/skin peeling/bleeding ulcer

Table 11: Acute skin reactions (cox et al)[48]

Grade 0	Nil
Grade 1	Slight atrophy /pigmentation change
Grade 2	Patch atrophy/moderate telangiectasia
Grade 3	Marked atrophy/gross telangiectasia
Grade 4	Ulceration

Table 12: Late skin reaction (Rubin P et al)

External beam radiotherapy boost to tumour bed has conventionally been thought to worsen the cosmesis. In the EORTC trial cosmesis was found to be significantly affected at a median follow-up of 10 years in patients who received radiotherapy boost whereas in the Budapest trial cosmesis was affected but the difference in two arms was not significant. Some studies have shown that a larger dose per fraction or a concomitant electron boost causes worsening of cosmesis but at the same time few others have denied the same[18,49–51].

It has also been shown that increasing inhomogeneities throughout the breast as well as boost volume also affects cosmesis adversely. Thus achieving a good homogenous distribution with newer techniques viz. IMRT may marginally improve the cosmesis (Vass *et al.*). Larger breasts, where cosmesis is known to be poorer, these techniques might help in avoiding hot as well as cold spots in the target volume. No significant difference in cosmetic outcome of patients receiving brachytherapy by various techniques such as electrons and tumor bed boost has been established. Though overall cosmesis rating was same in both the groups in most of the comparative studies telangiectasiae were more common in brachytherapy group[51–53]. Although Touboul et al. have found significantly poorer cosmesis in patients who received a brachytherapy boost; they have suggested it to be due to a combination of several factors. The patients in the brachytherapy group were mostly treated with Co^{60} (others were treated with 4–6 MV photons) and a higher percentage of these patients underwent axillary dissection[54].

The other factors which affect cosmesis adversely are administration of chemotherapy and axillary dissection[51].

Role of hypofractionated boost EBRT to tumor bed

Hypofractionated dose to tumor bed after whole breast irradiation is not well documented. There are few studies in this regard. The most commonly used fractionation scheme to treat tumor bed by EBRT is 16Gy / 8# or 10Gy/5# [32]. Janssen *et al.* (2014) demonstrated the efficacy of hypofractionated boost RT after hypofractionated WBI in 98 patients. Dose to whole breast was 41.6Gy in 13# followed by tumor bed boost of dose 9-12Gy in 3-4 #. Mean/ median follow up was 32/28 months. After 2 years local control, loco-regional control and disease-free survival was 100%, 100%, and 98%, respectively. Overall survival was 96% at 2 years. Cosmetic outcome was very good with patients being satisfied or very satisfied in 99% , 97% (n = 55/57) and 100% after one, two and four years after RT, respectively. Author concluded that hypofractionated regimen was well tolerated and effective on intermediate term follow up[55].

Author and Institute	Treatment	Year	RT dose	Conclusion
Wadasadawala *et al.*, (2009)[53] TMH, Mumbai	APBI vs WBRT highly favorable group of early breast cancer, i.e., tumor size up to 3 cm and absence of adverse radiologic or pathologic features (negative margins, no LVE or EIC, and negative nodes)	2000-2004	APBI- 34Gy/10# in 56-8 days WBRT- 45 Gy/25# followed by tumor bed boost, either with electrons (15 Gy/6#) or interstitial brachytherapy (HDR 10 Gy/1#)	At the median follow-up of 43.05 months in APBI and 51.08 months in WBRT there was no difference in overall survival (OS), disease-free survival (DFS), The cosmetic outcome was significantly better in the APBI group as compared to the WBRT group
Nandi M et al (2014)[56] Apollo Gleneagles Hospital Limited, KOLKATA	Hypofractionated RT to chest wall or whole breast and SCF	2011-2012	40Gy/15#	Cosmetic outcome in BCS patients remained good to excellent 6 months post surgery and radiotherapy.
Narayanan SS *et al.*, (2003)[57] TMH, Mumbai	Intraoperative HDR Ir-192 implant	2003	34Gy/10# in 5days	rigorous QA program, with serial imaging and dosimetry in the initial cohort of patients treated with radical intraoperative implants. Even when the technique is standardized and the variability parameters are known, the catheter

				fixation and exit catheter length should be measured daily
Rajan SS *et al.*, (2014)[58] Postgraduate Institute of Medical Education and Research, Chandigarh	Clinical and cosmetic results of breast boost radiotherapy in early breast cancer: a randomized study between electron and photon	2010-2011	WBI (40 Gy in 16 fractions) and then followed by tumor bed boost (16 Gy in 8 fractions) with either electron beam therapy or with photon (3DCRT)	overall cosmesis at 2 years is similar in both modalities

Table 13: Indian data on radiotherapy in early stage carcinoma breast

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