RECENT ADVANCES IN RADIATION IN BREAST CARCINOMA

Abstract

Breast cancer stands as the most prevalent form of cancer in India, carrying a significant mortality rate. Early diagnosis and prompt management play pivotal roles in diminishing both mortality and morbidity. The approach to breast cancer management is multidisciplinary, with surgery serving as the cornerstone of treatment. Chemotherapy is administered in neoadjuvant, adjuvant, and palliative settings, while radiation is employed adjuvantly or for palliative care. Targeted therapy is utilized in both adjuvant and palliative conditions.

Radiation is an integral component of breast-conservative treatment, its administration tailored to histopathological findings in mastectomy cases. The inclusion of a hypofractionated regimen in guidelines reflects contemporary practices. Ongoing trials seek to refine the treatment duration and target specifics.

This chapter delves into the advancements in treatment techniques.

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Breast cancer has taken over cervical cancer to become the most common cancer in India amongst women, accounting for 14% of all cancers in women (Figure 1). The incidence rate begins to rise in the early 30s and peaks at the age of 50-64 years. Despite availability of early screening tests and effective treatment options, one of two newly diagnosed women dies in India. There by necessitating further research in this area to fight this disease effectively.

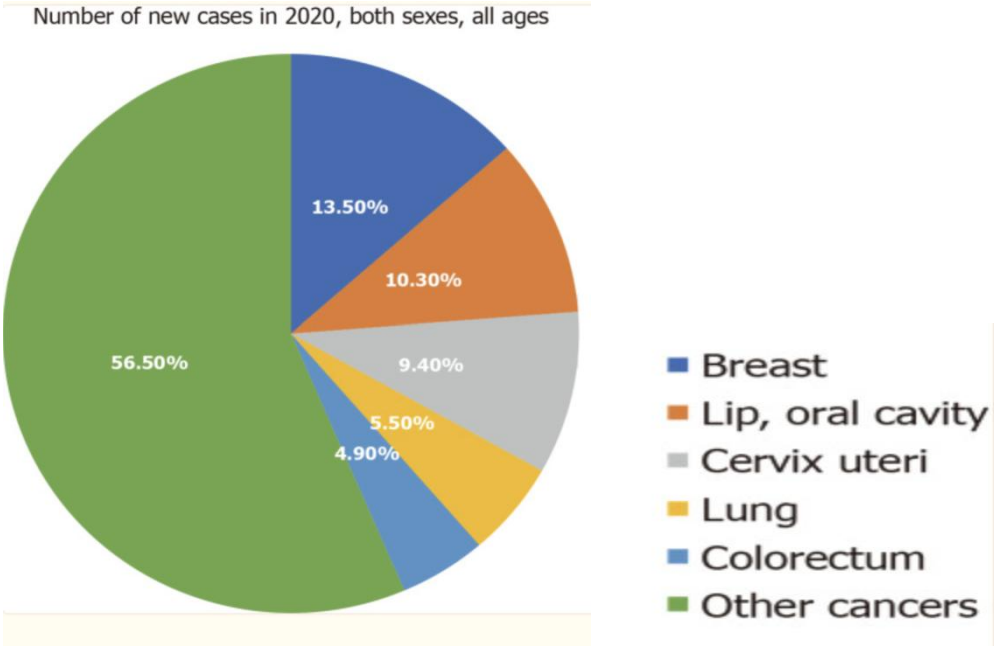

Figure 1

Radiation is an integral part of treatment of breast cancer in both early and late stages as well as in palliative cases. Advancements in the delivery techniques from 2 dimensional to 3 dimensional have not only reduced the overall treatment time but also have increased the therapeutic advantage by reducing the treatment field hence decreasing both acute and chronic toxicities.Apart from delivery techniques advancement has also been identified in fractionation schedules , cardiac sparing techniques as well as personalisation of radiation according to patient and tumor profile. In this chapter we will discuss the recent advancement in radiation in breast cancer.

I. FRACTIONATION SCHEDULE

With a long follow up of more than 20 years multiple randomized control studies have beyond doubt demonstrated that Breast conservation therapy is equivalent to mastectomy in terms of both local control and overall survival(1) . These studies mostly used standard(conventional) fractionation regimen with daily dose of 1.8-2 Gy per fraction for 5 to 7 weeks . The recent advancements have reduced this treatment duration by means of reduction of target size or increase in daily radiation dose.

Different options for delivering breast irradiation post BCS have been enumerated below.(Figure 2)

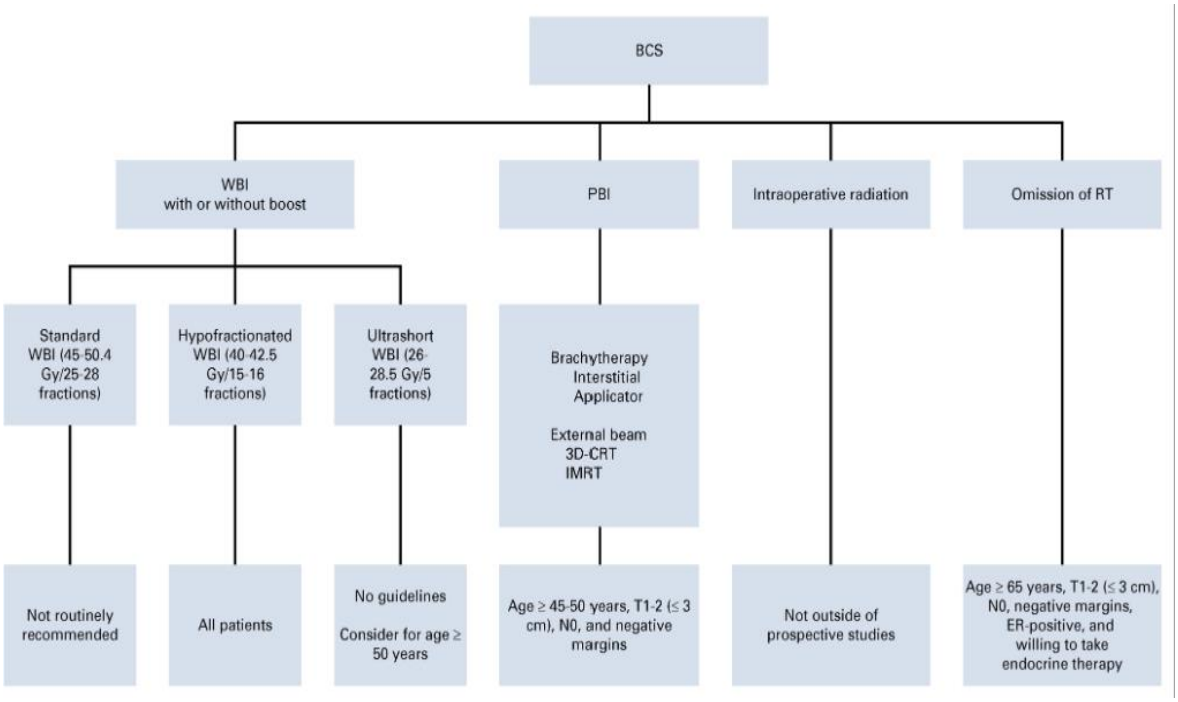

Figure 2

Multiple randomized controlled trials which have compared whole breast radiation via standard fractionation vs hypofractionation after a long term follow up have also shown similar survival and local control with comparable toxicity profile(2-3). In fact hypofractionation is now a standard practice in clinics these days for the treatment of both early and advanced cases as it is now incorporated in the treatment guidelines. A list of trials comparing standard fractionation to hypofractionation is as shown below (Table 1)

Table 1

Hypofractionation							
Trial	Years of Accrual	No. of Patients	F/U (years)	Radiation Dose	Local Recurrence with SWBI (%)	Local Recurrence with AWBI (%)	Toxicity
Ontario Oncology Group	1993-1996	1,234	12	42.56 Gy/16 fx 50 Gy/25 fx	6.2	6.7	No significant difference cosmetic outcomes (71.3% SWBI *v* 69.8% HWBI)
START-A	1999-2002	2,236	9.3	50 Gy/25 fx 41.6 Gy/13 fx 39 Gy/13 fx (all over 5 weeks)	6.7	5.6 8.1	No difference 50 Gy, 41.6 Gy with moderate or marked normal tissue effects; reduced induration/telangiectasia/edema with 39 Gy *v* 50 Gy
START-B	1999-2001	2,215	10	50 Gy/25 fx 40 Gy/15 fx	5.2	3.8	Breast shrinkage, telangiectasia, and edema significantly lower with 40 Gy

After inclusion of hypofractionation in the guidelines further research is being done in even shorter treatment regimens. FAST trial randomized patients with early breast cancer(pT1-2N0) into standard fractionation group and ultra hypofractionation group . Patients in ultrahypofractionation group received 28.5 Gy or 30 Gy in five fraction delivered once weekly without tumor bed boost.The three arms had comparable results with more toxicity in 30 Gy arm after a follow up of 10 years (4).Subsequently FAST forward trial which compared to standard hypofractionation to ultrahypofractionation (26-27 Gy in 5 fractions over 5 days) also found ultrahypofractionation to have similar tumor control as well as normal tissue effects(5) .

So the treatment delivery has shortened from around 2 months (as in conventional fractionation) to 5 days (ultrahypofractionation)in the appropriately selected patient population . Though a longer follow up is needed to study the result of ultrahypofractionation (Table2)

Table 2

Ultrashort Fractionation

Trial	Years of Accrual	No. of Patients	F/U (years)	Radiation Dose	Local Recurrence with Standard or Hypofractionated	Local Recurrence with Ultrashort	Toxicity
FAST	2004-2007	915	9.9	50 Gy/25 fx 30 Gy/5 fractions (once weekly) 28.5 Gy/5 fractions (once weekly)	Three recurrences	Four recurrences in 30 Gy and 28.5 Gy arms	OR moderate or marked normal tissue effects (*v* 50 Gy) 28.5 Gy: 1.22 30 Gy: 2.12
FAST-Forward	2011-2014	4,096	5.9	40 Gy/15 fx 27 Gy/5 fx 26 Gy/5 fx	2.1%	(*v* 40 Gy) 27 Gy: –0.3% 26 Gy: –0.7%	Moderate or marked normal tissue effects 40 Gy: 9.9% 26 Gy: 11.9% 27 Gy: 15.4%

II. TREATMENT TARGET

Whole breast radiation after BCS although improves treatment outcome but prolongs the treatment duration due to which patients belonging to lower socio economic classes quite often prefer mastectomy to avoid financial burden . In order to curtail this problem accelerated hypofractionation to small breast volume is done over 1-2 weeks . This is called accelerated partial breast irradiation (APBI) .

Rationale behind this is that recurrnec post BCS is usually localised to original quadrant Prospective trials have been done to compare Whole breast irradiation (WBI) to Partial breast irradiation (PBI) amongst which many have shown non significant difference in tumor control with PBI(6-17). The trials have been enumerated in the below mentioned table (Table 3)

Table 3

Partial Breast Irradiation

Trial	Years of Accrual	No. of Patients	F/U (years)	Radiation Dose/ Technique	Local Recurrence with WBI (%)	Local Recurrence with APBI (%)	Toxicity
National Institute of Oncology-Hungary	1998-2004	258	17	36.4 Gy/8 fx (interstitial) 50 Gy/25 fx (electrons)/ interstitial/electron	7.9	9.6	Improved cosmesis with APBI (81% *v* 63%)
GEC-ESTRO	2004-2009	1,184	6.6	32 Gy/8 fx 30.2 Gy/7 fx (HDR)/ 50 Gy (PDR)/ interstitial	0.9	1.4	Reduced late grade 2-3 skin toxicity with APBI
University of Florence	2005-2013	520	10.7	30 Gy/5 fx (every other day)/IMRT	2.5	3.7	Less acute and chronic toxicity with APBI
NSABP B39	2005-2013	4,216	10.2	38.5/10 fx 3D-CRT, 34 Gy/10 fx brachytherapy	3.9	4.6	Grade 3 toxicity: 10% APBI *v* 7% WBI
RAPID	2006-2011	2,135	8.6	38.5 Gy/10 fx/3D-CRT	2.8	3.0	Increased late toxicity with APBI (32% *v* 13%) and worse cosmesis with APBI
Barcelona	—	102	5.0	37.5 Gy/10 fx/3D-CRT	0	0	Lower rates of late toxicity with APBI and no difference in cosmesis
IMPORT LOW	2007-2010	2018	6.2	40 Gy/15 fx 36/15 fx (40/15 partial) 40/15 partial/3D-CRT	1.1 0.2	0.5	Similar photographic, patient, and clinical toxicity assessments, improved breast appearance, and firmness with partial breast

PBI delivered via brachytherapy has better cosmetic outcome than that delivered by external beam radiation as was seen in the RAPID trial , however no such difference was seen in subsequent trials (IMPORT low/NSABP-B39). In light of these findings selected patient subgroups are being treated by Partial breast irradiation .

ASTRO consensus describes three categories for suitability of APBI namely suitable , cautionary and unsuitable based on clinical and technical factors(18)(Table 4)

Table 4

Factors	Suitable (all factors)	Cautionary (any factor)	Unsuitable (any factor)
Age, years	≥50	40–49	<40
Tumor size, cm	≤2	2.1–3.0	>3
Histology type	Invasive ductal cancer	Invasive lobular cancer	Any
Histological/nuclear grade	Any DCIS: Grade 1 or 2	Any	Any
LVSI	No	Limited/focal	Extensive
EIC	No	≤3 cm	>3 cm
Pure DCIS	≤2.5 cm	≤3 cm	>3 cm
Estrogen receptor	Positive	Negative	-
Surgical margins	≥2 mm	<2 mm	Positive
Focality	Unicentric	-	-
Lymph Node Biopsy	Yes	-	No
Lymph Node Status	N0	Negative	Positive
BRCA Mutation	No	-	Positive
Neoadjuvant Chemotherapy	Not Allowed	Not Allowed	Yes

ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma *in situ*; EIC = extensive intraductal component; LVSI = lymphovascular space invasion; APBI = accelerated partial-breast irradiation.

APBI can be delivered by 1) interstitial brachytherapy 2) applicator based brachytherapy 3) External beam radiation

III. RADIATION FOR THE MANAGEMENT OF REGIONAL NODES

Historically all patients having clinically negative axilla after undergoing sentinel L.N biopsy when were found to have positive lymph nodes underwent complete axillary node dissection . however this paradigm was changed by AMAROS and ACOSOG ZOO11 trials and till date it is not advised for the omission of regional nodal irradiation even if a single node is found to be positive .

In patients who achieve complete response after Neoadjuvant chemotherapy are found to have lower local recurrence rate. NSABP51 trial aims to study omission of RNI in such patients . However the results are expected in years to come

IV. FUTURE DIRECTIONS

Despite extensive study being done in breast cancer treatment we have not been yet able to identify the set of patients in whom radiation could be completely omitted post Breast conservation surgery .The study of interplay of radiation and genetics may shed a light in this regard

V. REFERENCES

[1] Early Breast Cancer Trialists' Collaborative Group (EBCTG), Darby S, McGale P, et al: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data on 10,801 women in 17 randomised trials. Lancet 378:1707-1716, 2011 Crossref, Medline, Google Scholar

[2] .Whelan TJ, Pignol JP, Levine MN, et al: Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 362:513-520, 2010 Crossref, Medline, Google Schola

[3] Shaitelman SF, Schlembach PJ, Arzu I, et al: Acute and short-term toxic effects of conventionally fractionated vs. hypofractionated whole-breast irradiation: A randomized clinical trial. JAMA Oncol 1:931-941, 2015 Crossref,

[4] Brunt AM, Haviland JS, Sydenham M, et al: Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 38:3261-3272, 2020 Link, Google Scholar

[5] Brunt AM, Haviland JS, Wheatley DA, et al: Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicenter, non-inferiority, randomised, phase 3 trial. Lancet 395:1613-1626, 2020

[6] Shah C, Arthur D, Vicini F: Efficacy, improved quality of life, and cost-effectiveness of partial breast irradiation: A triple-threat approach. JAMA Oncol 6:1859-1860, 2020 Crossref, Medline, Google Scholar

[7] Polgar C, Major T, Takacsi-Nagy Z, et al: Breast-conserving surgery followed by partial or whole breast irradiation: Twenty-year results of a phase 3 clinical study. Int J Radiat Oncol Biol Phys 109:998-1006, 2021 Crossref, Medline, Google Scholar

[8] Strnad V, Ott OJ, Hildebrandt G, et al: 5-Year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: A randomised, phase 3, non-inferiority trial. Lancet 387:229-238, 2016

[9] Polgar C, Ott OJ, Hildebrandt G, et al: Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive an in-situ carcinoma of the female breast: 5-year results of a randomized, controlled, phase 3 trial. Lancet Oncol 18:259-268, 2017

[10] .Meattini I, Marrazzo L, Saieva C, et al: Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized Phase III APBI-IMRT-Florence trial. J Clin Oncol 38:4175-4183, 2020
[11] .Vicini FA, Cecchini RS, White JR, et al: Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: A randomised, phase 3, equivalence trial. Lancet 394:2155-2164, 2019
[12] Whelan TJ, Julian JA, Berrang TS, et al: External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): A randomised controlled trial. Lancet 394:2165-2172, 2019
[13] Rodriguez N, Sanz X, Dengra J, et al: Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 87:1051-1057, 2013
[14] Coles CE, Griffin CL, Kirby AM, et al: Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW): 5-Year results from a multicenter, randomized, controlled, phase 3, non-inferiority trial. Lancet 390:1048-1060, 2017
[15] Orecchia R, Veronesi U, Masionneuve P, et al: Intraoperative irradiation for early breast cancer (ELIOT): Long-term recurrence and survival outcomes from a single-centre randomised, phase 3 equivalence trial. Lancet Oncol 22:597-608, 2021
[16] Vaidya JS, Bulsara M, Saunders C, et al: Effect of delayed targeted intraoperative radiotherapy vs whole-breast radiotherapy on local recurrence and survival: Long-term results from the TARGIT-A randomized clinical trial in early breast cancer. JAMA Oncol 6:e200249, 2020
[17] .Vaidya JS, Bulsara M, Baum M, et al: Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial.
[18] ASTRO Consensus Statement on APBI for Breast Cancer Oncology Times 31(17):p 11, September 10, 2009.

