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Review Article

Adjuvant radiation therapy in breast cancer: Recent advances & Indian data

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Breast cancer is the most common cancer among women in India, and adjuvant radiotherapy is an integral part of curative treatment in most patients. The recent decades have witnessed several advances in radiation therapy delivery. Several advances in radiation oncology have been identified which include technological advances, change in fractionation used, use of cardiac-sparing radiotherapy as well as efforts to personalize radiotherapy using accelerated partial breast irradiation or avoidance of radiotherapy in certain subpopulations. Indian data are available in most areas which have been summarized. However, increasing emphasis on research in these areas is needed so that effectiveness and safety in our setting can be established. Advances in breast cancer radiotherapy have resulted in improved outcomes. Data published from India suggest that these improved outcomes can be replicated in patients when appropriate treatment protocols are followed.

Key words Breast cancer - cardiac sparing - DIBH - hypofractionation - IMR - PBI - radiation avoidance - radiotherapy - SIB

Breast cancer is the most common cancer among women in India, and about 160,000 cases are diagnosed annually[1]. It is also the most common cause of cancer-related mortality and disability in India[2]. Adjuvant radiotherapy plays an important role in the breast cancer management paradigm. Results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis in patients undergoing breast conservation surgery showed that the risk of use of adjuvant radiotherapy resulted in a 50 per cent relative reduction in the risk of a locoregional recurrence at 15 years[3]. Similarly, in node-positive patients undergoing mastectomy, the use of adjuvant radiotherapy translated into a relative risk reduction in locoregional recurrence at 10 yr to the tune of 69 per cent[4]. More importantly, in the patients undergoing breast conservation, one breast cancer death was avoided at 15 yr for every four locoregional recurrences avoided, while in patients who had undergone a mastectomy[4], one breast cancer death was avoided at 20 yr for every 1.5 locoregional recurrences avoided[3].

Over the past couple of decades, advances in technology, as well as our understanding of breast cancer biology, coupled with an increasing emphasis on early detection, have resulted in improved outcomes for breast cancer patients. A larger proportion of patients now undergo breast conservation surgery, and the issues related to the quality of life and survivorship care are receiving much-needed attention. Here, an attempt was made to review the recent advances made in adjuvant radiotherapy of breast cancer and also to look at the Indian data in these areas. After internal discussion among ourselves, as well as the experience with a recently concluded expert consensus meeting in breast cancers, the following areas were identified: (*i*) Technological advances in dose delivery: better dose homogenization and development of simultaneous-integrated boost (SIB) techniques; (*ii*) widespread use of altered fractionation, *e.g.,* hypofractionation; (*iii*) avoidance of morbidity of radiation therapy, especially cardiac morbidity; (*iv*) customization of irradiation volume, *e.g.,* avoidance of whole-breast irradiation; and (*v*) avoidance of radiation therapy in certain low-risk populations.

Technological advances

Intensity-modulated radiotherapy (IMRT): Radiation to the breast is complicated by the anatomy and the relationship of the primary target volume (*i.e.,* chest wall or breast) as well as the elective nodal volumes with the underlying organs at risk. Furthermore, given the relatively favourable prognosis of breast cancer, restricting the irradiated volume to reduce the risk of contralateral breast and lung cancers is an important planning target. Hence, the most common beam arrangement used to ensure optimal dose delivery is a tangential beam pair for the breast/chest wall along with *en face* portals for regional nodes. Most modern radiotherapy trials have avoided axillary radiotherapy after adequate axillary dissection as isolated axillary recurrence rates are low and lymphedema risks are high[5,6]. Use of forward planned IMRT, has been investigated in several randomized controlled trials. In the earliest reported trial by Donovan *et al*[7], the use of IMRT reduced the incidence of change in breast appearance. Pignol *et al*[8] demonstrated a significantly reduced risk of moist desquamation after radiotherapy. Two and five-year follow up results of the Cambridge Breast Forward-Planned IMRT Trial reported a significant reduction in the risk of developing telangiectasia as well as improved cosmesis in patients undergoing IMRT[9,10].

Prabhakar *et al*[11,12] reported a significant reduction in contralateral breast dose with the use of IMRT as compared to standard wedged tangential fields. Kataria *et al*[13] reported a lower incidental dose to the axilla with the use of forward-planned IMRT and three-dimensional conformal radiotherapy (3DCRT) as compared to the standard technique. No clinical studies comparing outcomes in IMRT and 3DCRT have been reported from India. Several dosimetric studies have examined the feasibility of using volumetric modulated arc therapy (VMAT) instead of tangents and have reported better coverage of the breast/chest wall target volume[14,15]. Of these, an *in silico* trial reported a significant increase in the contralateral breast dose with the use of these techniques[14]. None of these studies have reported comparative clinical outcomes.

Simultaneous Integrated Boost: Incorporation of the tumour bed boost after conventional breast irradiation results in prolongation of the overall treatment time by almost one and a half weeks, stretching the total treatment time to around six and a half weeks. As a result, several studies have attempted to incorporate the tumour bed boost along with the course of whole-breast irradiation - a technique of treatment delivery called simultaneous integrated boost (SIB). Table I shows a summary of the results obtained from prospective studies that have evaluated the outcomes of a SIB strategy in breast cancers[16-20]. Good cosmesis and local control were reported across all these studies. The largest trial investigating a SIB strategy in breast cancers with a higher risk of recurrence (IMPORT High) has demonstrated that the use of a SIB strategy with a dose schedule of 48 Gy delivered to tumour bed results in no significant difference in grade 3/4 adverse events as compared to a sequential boost strategy[21].

In two studies on SIB from India, IMRT using a VMAT technique or a seven-field IMRT technique was utilized to irradiate the entire breast and regional nodes with tumour bed boost. An electron boost was used by Jalali *et al*[22]. The largest study reported by Dewan *et al*[23] had 223 patients treated to a total dose of 59.92 Gy in 28 fractions (#) with a non-standard dose fractionation regimen for the whole-breast/regional nodes (46 Gy in 28 fractions). They reported grade 2-3 acute skin toxicity in 31 per cent patients, while chronic grade 2-3 fibrosis was reported in 16 per cent of the patients. Only one patient had a local recurrence at a median follow up of 18 months. Two other studies explored the use of helical tomotherapy for treatment of the bilateral breast cancers with an SIB to the tumour bed[24,25]. However, the use of rotational or multi-field IMRT techniques can result in a higher dose to contralateral breast and lung as shown by Joseph *et al*[26].

To combine the advantages of tangential breast radiation with the dose conformity obtained by using

Table I. Treatment techniques and outcomes of studies investigating simultaneous integrated boost

Author (year)	n	Technique	FU	Local control (%)	Good cosmesis (%)
Franco *et al*[16], 2014	82	Tomotherapy (whole breast + boost)	12	100	91
Cooper *et al*[17], 2016	400	Prone tangential + IMRT boost	45	99	80
De Rose *et al*[18], 2016	144	VMAT (whole breast + tumor bed)	37	100	NA
Shin *et al*[19], 2016	45	Prone 3 field IMRT	36	100	85
Cante *et al*[20], 2017	178	Tangential+direct photon boost	117	97.3	87.80

Studies which reported medium to long-term outcomes included. FU, follow up in years; RT, radiotherapy; IMRT, intensity modulated RT; VMAT, volumetric-modulated arc therapy

IMRT, our team developed a SIB class solution[27]. This technique emphasizes conformal avoidance of normal tissues, especially contralateral lung and breast, while improving conformity of the high-dose region in the breast. To achieve this, a tangential field-in-field forward-planned IMRT technique is used for whole-breast irradiation to homogenize the dose distribution. The tumour bed boost is delivered using a pair of short VMAT arcs of 25°-30° offset at an angle of 10°-15° from the tangents[27].

Dosimetric comparison between a traditional sequential boost class and SIB class solution shows improved target dose conformity (conformity index 0.52 in SIB *vs*. 0.31 with sequential boost) while maintaining conformal avoidance of contralateral organs at risk (Table II).

Altered fractionation

Moderate hypofractionation: Conventional breast radiotherapy is delivered over a period of 5-6 wk using a dose fractionation of 1.8-2 Gy per fraction in the USA[28]. This stemmed from the belief that breast cancer had fraction sensitivity similar to that of other cancers, notably squamous cell carcinomas. Unfortunately, the prolonged duration of radiation was a significant hindrance in the uptake of breast conservation in breast cancer[28] and was associated with a limited access to radiotherapy with consequent increase in the risk of local recurrence[29]. Research on alternate fractionation schedules where a higher dose of radiation was delivered over a shorter period of time (known as hypofractionation) was first undertaken at the Royal Marsden Hospital and Gloucestershire Oncology Center, UK in 1998[30]. The results showed that breast cancer behaved similar to late reacting normal tissues - with the implication that a higher than conventional dose fractionation was likely to result in the similar local control without excess toxicity if the total dose was appropriately adjusted[31]. Following this trial, three seminal trials were reported from Canada and the UK in which various hypofractionated radiotherapy schedules were investigated in nearly 8000 women[30,32]. Taken together, the trials demonstrated the safety and effectiveness of hypofractionated radiotherapy delivered over 15-16 fractions with appropriate reduction in total radiation dose. The results from the START B trial demonstrated that use of the 40 Gy/15#/three-week regimen was associated with a significantly reduced risk of late normal tissue complications[30]. Another study of hypofractionated radiotherapy after mastectomy also demonstrated non-inferiority of the hypofractionated radiotherapy schedule[33].

The results of studies on moderate hypofractionation from India are summarized in Table III. The largest study reported is by Chatterjee *et al*[34], who have reported outcomes of more than 900 patients treated with a uniform protocol of 40 Gy/15#/three-week regimen with an excellent local control comparable to results obtained in the START trial[30]. The acute toxicity reported by the same group was also comparable with end of treatment grade 2 toxicity being reported by six per cent of patients who had undergone mastectomy and 23 per cent in patients who had undergone breast conservation[41]. Late effects of use of moderate hypofractionation have been reported by Yadav *et al*[42]. Overall results from the Indian subcontinent showed similar outcomes with moderately hypofractionated radiotherapy as compared to stage-matched patients from the West[34].

Extreme hypofractionation: Given the results of hypofractionated radiotherapy, it has been reported that earlier further hypofractionation with compression of treatment intervals to one week may be appropriate[43,44]. Two studies were published till date where a five-fraction regimen was compared to a conventional regimen. The UK FAST study reported 10 yr outcomes of a five-fraction schedule delivered over one week and

Table II. Comparison between simultaneous integrated boost (SIB) and sequential (SEQ) plans for various volumes

Volume	Dosimetric parameter	SIB technique	SEQ technique	*P*
BTV	D98* (%)	95.5 (94.7-96.4)	94.9 (94.0-95.9)	0.38
	D2† (%)	103.2 (102.5-103.9)	102.9 (102.0-103.8)	0.85
	Conformity index	0.52 (0.47-0.56)	0.31 (0.28-0.35)	<0.01
	Homogeneity index	0.08 (0.07-0.08)	0.08 (0.07-0.09)	0.44
	V95‡ (%)	97.9 (96.9-98.9)	97.7 (97.0-98.7)	0.88
Contralateral breast	$D_{mean\#}$ (Gy)	0.25 (0.17-0.32)	0.12 (0.10-0.15)	<0.01
	V0.5ǁ (%)	14.1 (10.5-17.8)	7.7 (5.8-9.6)	<0.01
Contralateral lung	$D_{mean\#}$ (Gy)	0.16 (0.13-0.19)	0.14 (0.12-0.17)	<0.01
	V0.5ǁ (%)	4.9 (3.4-6.4)	3.4 (2.0-4.8)	<0.01
Heart	$D_{mean\#}$ (Gy)	0.90 (0.73-1.07)	0.87 (0.69-1.04)	0.01
	V0.5ǁ (%)	56.5 (48.8-64.1)	53.5 (43.6-63.4)	0.03
Ipsilateral lung	V12§ (%)	15.8 (13.1-18.4)	15.6 (12.9-18.4)	0.12
	$D_{mean\#}$ (Gy)	6.64 (5.80-7.49)	6.66 (5.79-7.54)	0.81

Figures represent the mean and 95 per cent confidence interval. *Dose to 98 per cent volume; †Dose to 2 per cent volume; ‡Percentage volume receiving 95 per cent prescribed dose; #Mean dose to volume; ǁPercentage volume receiving 0.5 Gy dose; §Percentage volume receiving 12 Gy. BTV, boost target volume

Table III. Compilation of results of hypofractionated radiotherapy in breast cancer reported from India

Author (year)	n	Dose fractionation	Follow up (months)	Local control (%)	Overall survival (%)
Chatterjee *et al*[34], 2016	925	40 Gy/15#	22	97.1*	93
Mishra *et al*[35], 2016	56	42.4 Gy/16#	11	96.5	NA
Chelakkot *et al*[36], 2017	308	40 Gy/15#	60	99.45	81
Yadav and Sharma[37], 2018	50	34 Gy/10#	39	100	96
Rastogi *et al*[38], 2018	50	42.72 Gy/15#	20	100	100
Yadav *et al*[39], 2020	254	42.4 Gy/16#	46	97*	NA
Vijayaraghavan *et al*[40], 2020	67	42.5 Gy/16#	9	98.5	NA

*Studies have reported locoregional recurrence-free survival instead of local recurrence-free survival. NA, not available

showed that the regimen of 28.5 Gy in five fractions was well tolerated and associated with similar rates of late toxicity[43,44]. However, the patient population studied in the trial was primarily of early breast cancers, and the relevance of this study in the Indian settings remains doubtful as the overall treatment time extends to five weeks[45]. Moreover, the trial[45] was not designed to test for difference in relapse rates between the two arms, but overall local relapse rate was only 1.3 per cent in the 917 patients recruited in the study. The larger FAST Forward Trial compared two-dose schedules of 26 and 27 Gy (over five fractions in one week) against the standard 40 Gy/15# regimen (delivered over three weeks)[46]. Acute toxicity results reported from the study suggested no increase in acute skin toxicity with 26 Gy schedule as compared to the 40 Gy schedule[46]. Long-term outcome data suggest that the use of this schedule is non-inferior in properly selected early-stage low-risk breast cancer patients[47].

None of the studies form India compared a five-fraction regimen against a standard treatment approach. However, an ongoing study HYPORT Adjuvant (CTRI/2018/12/016816/Clinical Trials: NCT03788213) is testing a 26 Gy/5#/one-week regimen against a 40 Gy/15#/three-week standard schedule[43,48]. In addition, patients who have undergone breast conservation are also being treated with an SIB to give a one-week treatment regimen.

Cardiac sparing

In the past decade, increasing attention has been focussed on the importance of avoiding cardiac morbidity (and mortality) in patients with breast cancer.

Cardiovascular disease is a major contributor towards morality in breast cancer patients and among women between 70 and 79 yr and accounts for 22 per cent of the deaths (while breast cancer itself accounts for 17 per cent of the deaths by 10 yr)[49]. Darby *et al*[50] have reported that each Gy increase in the mean heart dose raises the risk of major cardiac events by 7.4 Gy, with no apparent lower threshold. Radiotherapy-induced heart disease (RIHD) is a complex, multifactorial disorder, and currently, the primary pathophysiology is believed to be radiation-induced endothelial injury resulting in microvascular occlusion and consequent myocardial ischemia. It is believed that the inflammatory response due to endothelial injury accelerates macrovascular atherosclerosis[51]. A dose relationship for the left anterior descending artery was proposed where a mean dose greater than 20 Gy was shown to be associated with an increased risk of developing coronary stenosis (odds ratio of 5.23)[52].

Modern radiation techniques have been developed to allow safer cardiac-sparing radiotherapy[53]. The two most commonly used techniques include prone breast radiotherapy and deep inspiration breath-hold (DIBH). A recent survey of radiation oncologists in the USA showed that the DIBH was most commonly used to spare the heart[54]. DIBH is a form of radiotherapy delivery where radiation is delivered while the patient breathes in deeply and holds the breath. As a consequence, the heart rotates inwards inside the thorax and becomes more tubular as the diaphragm moves down, reducing cardiac dose. Analysis of results collated in a systematic review shows a weighted average absolute reduction of 2.1 and 5.9 Gy in the mean cardiac dose and mean left anterior descending artery dose, respectively, when DIBH is used[55]. This corresponds to halving of the dose as compared to that received in the free-breathing plans.

All of the eight studies on cardiac sparing from India were dosimetric studies which reported a mean heart dose reduction ranging between 50 and 60 per cent as compared to free-breathing plans[56-63]. Chatterjee *et al*[60] quantified the resource utilization and the cost-effectiveness of using DIBH for all left-sided breast cancers. They found that the use of DIBH resulted in a reduction of 0.95 yr of life lost (YLL) per 100 patients treated (0.09 per patient). These estimates were relatively similar to those reported by Simonetto *et al*[64] from the Netherlands who reported that the use of DIBH resulted in a reduction of YLL between 0.09 and 0.02 per patient. DIBH was found to be cost-effective in the Indian setting even when higher estimates of salary as prevalent in the private sector were taken into the account[60].

New treatment volume concepts

Partial breast irradiation (PBI): While whole-breast radiotherapy improves outcomes after breast conservation surgery, prolonged treatment is often a concern. As a consequence, patients with poor socio-economic status and those residing in countries with limited access to radiotherapy will often forego breast conservation[65,66]. As most recurrences after breast conservation surgery are usually confined within the original quadrant[67,68], there is a rationale to treat a small volume of breast hence, the name partial breast irradiation (PBI). Given the volume effects associated with radiotherapy, the small target volume allows accelerated hypofractionated radiotherapy schedules to be used with radiation being delivered to a small volume in 1-2 wk often treating twice a day[69]. This type of radiation is known as APBI. Various techniques have been used including 3DCRT[21,70], single and multi-catheter brachytherapy[71,72], as well as intraoperative radiotherapy[73,74].

Clinical outcomes of several randomized controlled trials have been reported which have utilized various techniques for delivery of APBI making cross-trial comparisons difficult[69]. Comparison of outcomes in randomized controlled trials that have investigated PBI against whole-breast irradiation suggests that local recurrence rates may be higher[75,76]. However, a meta-analysis showed that external beam radiotherapy-based PBI techniques might be associated with the lowest margin for non-inferiority[76]. Further risk of fat necrosis was also found to be higher in patients undergoing APBI[76]. Overall, the results of these studies suggest that careful case selection and attention to quality are essential for safe implementation of APBI in clinical practice.

While 23 studies were identified which reported results of PBI, mature clinical outcome data were available from one institute (Wadasadawala & colleagues)[77,78] where a multi-catheter PBI technique was followed. Clinical, cosmetic and patient-reported outcomes were favourable, with better outcomes reported for cosmesis and patient-reported outcomes with APBI as compared to whole-breast irradiation[77-79]. Perioperative implant placement was generally favoured. Five- and seven-year local control rates

Table IV. Summary outcomes of two trials evaluating avoidance of adjuvant radiotherapy

Study	n	Age (yr)	T size (cm)	N+	FU	LRFS (%)	OS (%)
CALGB 9343[83]	636	≥70	≤2	No	10	RT: 98 No RT: 90	RT: 67 No RT: 66
PRIME II[84]	658	≥65	≤3	No	5	RT: 98.7 No RT: 95.9	RT: 93.9 No RT: 93.9

Superscript numerals denote reference numbers. n, number; T size, tumour size; N+, node positive allowed; FU, follow up in years; LRFS, local recurrence-free survival; OS, overall survival; RT, radiotherapy

were 97 and 92 per cent[80]. Excellent-to-good cosmesis was reported in 77 per cent of women[80]. Dosimetric comparison of an external beam-based APBI technique against whole-breast irradiation has been reported by Kumar *et al*[81] who reported that the use of 3DCRT APBI approach resulted in improved conformity as compared to whole-breast tangents. The key issues with implementing these treatment techniques in most centres in India are lack of expertise for brachytherapy-based PBI, as well as the necessary caseload of patients eligible for APBI. Further, the role of multi-catheter APBI (especially the perioperative technique) has not been well studied in patients undergoing oncoplastic breast surgery[82].

Radiation avoidance: With improvement in outcomes of patients with breast cancer, the risk of locoregional recurrence has declined. As a result, increasing attention is now being focussed on avoidance of adjuvant radiotherapy in selected patients with a low risk of recurrence. Two randomized controlled trials have investigated omission of adjuvant radiotherapy in elderly patients undergoing breast conservation[83,84]. In both these studies, a favourable population of elderly patients, with T1-T2 tumours and luminal type A disease subtype, were selected. The results of these trials are summarized in Table IV. As can be seen, there was a significant increase in the local recurrence rate with the avoidance of radiotherapy in these studies. While the results of these two studies[83,84] show that there is no detriment in overall survival with avoidance of adjuvant radiotherapy in subset of patients with low-risk disease, the applicability of these findings in the Indian setting needs to be seen where the prevalence of such early-stage low-grade disease is low and adherence to long-term follow up may be a problem. Furthermore, with increasing adoption of hypofractionated radiotherapy and cardiac-sparing techniques, the primary concerns with adjuvant radiotherapy usage even in this population may be rendered moot[85].

Conclusion

Most institutes that have adopted hypofractionated radiotherapy have been able to report good outcomes. This has important implications for India, where radiotherapy resources are limited. Further adoption of hypofractionation results in significant cost savings for the patient. Institutional practice varies widely with respect to more sophisticated techniques such as cardiac-sparing radiotherapy, SIB, and APBI, but centres that have adopted these techniques in a systematic manner have reported comparable outcomes as in West. There is need for developing multi-centric collaborative research studies to identify gaps in knowledge where such research would be most useful.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021: *71* : 209- 49.
2. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: The Global Burden of Disease Study 1990-2016. *Lancet Oncol* 2018; *19* : 1289-306.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, Correa C, Taylor C, Arriagada R, *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 for 10,801 women in 17 randomised trials. *Lancet* 2011; *378* : 1707-16.

4. EBCTCG (Early Breast Cancer Trialists' Collaborative Group); McGale P, Taylor C, Correa C, Cutter D, Duane F, *et al*. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; *383* : 2127-35.

5. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, *et al*. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; *373* : 317-27.

6. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, *et al*. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015; *373* : 307-16.

7. Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, *et al*. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radiother Oncol* 2007; *82* : 254-64.

8. Pignol JP, Olivotto I, Rakovitch E, Gardner S, Sixel K, Beckham W, *et al*. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008; *26* : 2085-92.

9. Barnett GC, Wilkinson JS, Moody AM, Wilson CB, Twyman N, Wishart GC, *et al*. Randomized controlled trial of forward-planned intensity modulated radiotherapy for early breast cancer: Interim results at 2 years. *Int J Radiat Oncol Biol Phys* 2012; *82* : 715-23.

10. Mukesh MB, Barnett GC, Wilkinson JS, Moody AM, Wilson C, Dorling L, *et al*. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol* 2013; *31* : 4488-95.

11. Prabhakar R, Julka PK, Malik M, Ganesh T, Joshi RC, Sridhar PS, *et al*. Comparison of contralateral breast dose for various tangential field techniques in clinical radiotherapy. *Technol Cancer Res Treat* 2007; *6* : 135-8.

12. Prabhakar R, Haresh KP, Julka PK, Ganesh T, Rath GK, Joshi RC, *et al*. A study on contralateral breast surface dose for various tangential field techniques and the impact of set-up error on this dose. *Australas Phys Eng Sci Med* 2007; *30* : 42-5.

13. Kataria T, Bisht SS, Gupta D, Goyal S, Jassal K, Abhishek A, *et al*. Incidental radiation to axilla in early breast cancer treated with intensity modulated tangents and comparison with conventional and 3D conformal tangents. *Breast* 2013; *22* : 1125-9.

14. Khullar P, Garg C, Sinha SN, Kaur I, Datta NR. An *in silico* comparative dosimetric study of postmastectomy locoregional irradiation using intensity-modulated vs. 3-dimensional conventional radiotherapy. *Med Dosim* 2018; *43* : 370-6.

15. Sudha SP, Seenisamy R, Bharadhwaj K. Comparison of dosimetric parameters of volumetric modulated arc therapy and three-dimensional conformal radiotherapy in postmastectomy patients with carcinoma breast. *J Cancer Res Ther* 2018; *14* : 1005-9.

16. Franco P, Zeverino M, Migliaccio F, Cante D, Sciacero P, Casanova Borca V, *et al*. Intensity-modulated and hypofractionated simultaneous integrated boost adjuvant breast radiation employing statics ports of tomotherapy (TomoDirect): A prospective phase II trial. *J Cancer Res Clin Oncol* 2014; *140* : 167-77.

17. Cooper BT, Formenti-Ujlaki GF, Li X, Shin SM, Fenton-Kerimian M, Guth A, *et al*. Prospective randomized trial of prone accelerated intensity modulated breast radiation therapy with a daily versus weekly boost to the tumor bed. *Int J Radiat Oncol Biol Phys* 2016; *95* : 571-8.

18. De Rose F, Fogliata A, Franceschini D, Navarria P, Villa E, Iftode C, *et al*. Phase II trial of hypofractionated VMAT-based treatment for early stage breast cancer: 2-year toxicity and clinical results. *Radiat Oncol* 2016; *11* : 120.

19. Shin SM, No HS, Vega RM, Fenton-Kerimian M, Maisonet O, Hitchen C, *et al*. Breast, chest wall, and nodal irradiation with prone set-up: Results of a hypofractionated trial with a median follow-up of 35 months. *Pract Radiat Oncol* 2016; *6* : e81-8.

20. Cante D, Petrucci E, Sciacero P, Piva C, Ferrario S, Bagnera S, *et al*. Ten-year results of accelerated hypofractionated adjuvant whole-breast radiation with concomitant boost to the lumpectomy cavity after conserving surgery for early breast cancer. *Med Oncol* 2017; *34* : 152.

21. Coles CE, Griffin CL, Kirby AM, Haviland JS, Titley JC, Benstead K, *et al*. Abstract GS4-05: Dose escalated simultaneous integrated boost radiotherapy for women treated by breast conservation surgery for early breast cancer: 3-year adverse effects in the IMPORT HIGH trial (CRUK/06/003). *Cancer Res* 2019; *79* (Suppl 4): GS4-05.

22. Jalali R, Malde R, Bhutani R, Budrukkar A, Badwe R, Sarin R. Prospective evaluation of concomitant tumour bed boost with whole breast irradiation in patients with locally advanced breast cancer undergoing breast-conserving therapy. *Breast* 2008; *17* : 64-70.

23. Dewan A, Chufal KS, Dewan AK, Pahuja A, Mehrotra K, Singh R, *et al*. Simultaneous integrated boost by Intensity Modulated Radiotherapy (SIB-IMRT) in patients undergoing breast conserving surgery – A clinical and dosimetric perspective. *J Egypt Natl Canc Inst* 2018; *30* : 165-71.

24. Wadasadawala T, Visariya B, Sarin R, Upreti RR, Paul S, Phurailatpam R. Use of tomotherapy in treatment of synchronous bilateral breast cancer: Dosimetric comparison study. *Br J Radiol* 2015; *88* : 20140612.

25. Wadasadawala T, Jain S, Paul S, Phurailatpam R, Joshi K, Popat P, *et al*. First clinical report of helical tomotherapy with simultaneous integrated boost for synchronous bilateral breast cancer. *Br J Radiol* 2017; *90* : 20170152.

26. Joseph B, Farooq N, Kumar S, Vijay CR, Puthur KJ, Ramesh C, *et al*. Breast-conserving radiotherapy with simultaneous integrated boost; field-in-field three-dimensional conformal radiotherapy versus inverse intensity-modulated radiotherapy – A dosimetric comparison: Do we need intensity-modulated radiotherapy? *South Asian J Cancer* 2018; *7* : 163-6.

27. Chatterjee S, Mahata A, Mandal S, Chakraborty S. Simultaneous integrated boost: Improving the patient journey during breast cancer radiotherapy safely. *Clin Oncol* 2019; *31* : 266.

28. Lam J, Cook T, Foster S, Poon R, Milross C, Sundaresan P. Examining determinants of radiotherapy access: Do cost and radiotherapy inconvenience affect uptake of breast-conserving treatment for early breast cancer? *Clin Oncol* 2015; *27* : 465-71.

29. Punglia RS, Saito AM, Neville BA, Earle CC, Weeks JC. Impact of interval from breast conserving surgery to radiotherapy on local recurrence in older women with breast cancer: Retrospective cohort analysis. *BMJ* 2010; *340* : c845.

30. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, *et al*. The UK standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; *14* : 1086-94.

31. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, *et al*. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: Long-term results of a randomised trial. *Lancet Oncol* 2006; *7* : 467-71.

32. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, *et al*. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; *362* : 513-20.

33. Wang SL, Fang H, Song YW, Wang WH, Hu C, Liu YP, *et al*. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: A randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* 2019; *20* : 352-60.

34. Chatterjee S, Arunsingh M, Agrawal S, Dabkara D, Mahata A, Arun I, *et al*. Outcomes following a moderately hypofractionated adjuvant radiation (START B Type) schedule for breast cancer in an unscreened non-caucasian population. *Clin Oncol* 2016; *28* : e165-72.

35. Mishra R, Khurana R, Mishra H, Rastogi M, Hadi R. Retrospective analysis of efficacy and toxicity of hypo-fractionated radiotherapy in breast carcinoma. *J Clin Diagn Res* 2016; *10* : XC01-3.

36. Chelakkot GP, Ravind R, Sruthi K, Chigurupati N, Kotne S, Holla R, *et al*. Adjuvant hypofractionated radiation in carcinoma breast – Photon versus electron: Comparison of treatment outcome. *J Cancer Res Ther* 2017; *13* : 262-7.

37. Yadav BS, Sharma SC. A phase 2 study of 2 weeks of adjuvant whole breast/chest wall and/or regional nodal radiation therapy for patients with breast cancer. *Int J Radiat Oncol Biol Phys* 2018; *100* : 874-81.

38. Rastogi K, Jain S, Bhatnagar AR, Bhaskar S, Gupta S, Sharma N. A comparative study of hypofractionated and conventional radiotherapy in postmastectomy breast cancer patients. *Asia Pac J Oncol Nurs* 2018; *5* : 107-13.

39. Yadav R, Lal P, Agarwal S, Misra S, Verma M, Das KJ, *et al*. Comparative retrospective analysis of locoregional recurrence in unselected breast cancer patients treated with conventional versus hypofractionated radiotherapy at a tertiary cancer center? *J Cancer Res Ther* 2020; *16* : 1314-22.

40. Vijayaraghavan N, Vedasoundaram P, Mathew JM, Menon A, Kannan B. Assessment of acute toxicities and early local recurrences in post mastectomy breast cancer patients by accelerated hypofractionated radiotherapy; a single arm clinical trial. *J BUON* 2020; *25* : 2265-70.

41. Nandi M, Mahata A, Mallick I, Achari R, Chatterjee S. Hypofractionated radiotherapy for breast cancers – Preliminary results from a tertiary care center in eastern India. *Asian Pac J Cancer Prev* 2014; *15* : 2505-10.

42. Yadav BS, Bansal A, Kuttikat PG, Das D, Gupta A, Dahiya D. Late-term effects of hypofractionated chest wall and regional nodal radiotherapy with two-dimensional technique in patients with breast cancer. *Radiat Oncol J* 2020; *38* : 109-18.

43. Brunt AM, Haviland J, Sydenham M, Algurafi H, Alhasso A, Bliss P, *et al*. FAST Phase III RCT of radiotherapy hypofractionation for treatment of early breast cancer: 10-year results (CRUKE/04/015). Available from: *https://www.redjournal.org/article/S0360-3016(18)33691-5/abstract*, accessed on March 1, 2020.

44. FAST Trialists Group; Agrawal RK, Alhasso A, Barrett-Lee PJ, Bliss JM, Bliss P, *et al*. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). *Radiother Oncol* 2011; *100* : 93-100.

45. Chakraborty S, Wadasadawala T, Ahmed R, Coles C, Chatterjee S. Breast cancer demographics, types and management pathways: Can western algorithms be optimally used in eastern countries? *Clin Oncol* 2019; *31* : 502-9.

46. Brunt AM, Wheatley D, Yarnold J, Somaiah N, Kelly S, Harnett A, *et al*. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward trial. *Radiother Oncol* 2016; *120* : 114-8.

47. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, *et al*. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* 2020; *395* : 1613-26.

48. Chatterjee S, Chakraborty S; HYPORT Adjuvant Author Group. Hypofractionated radiation therapy comparing a standard radiotherapy schedule (over 3 weeks) with a novel 1-week schedule in adjuvant breast cancer: An open-label randomized controlled study (HYPORT-Adjuvant)-study protocol for a multicentre, randomized phase III trial. *Trials* 2020; *21* : 819.

49. Park NJ, Chang Y, Bender C, Conley Y, Chlebowski RT, van Londen GJ, *et al*. Cardiovascular disease and mortality after breast cancer in postmenopausal women: Results from the Women's Health Initiative. *PLoS One* 2017; *12* : e0184174.

50. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, *et al*. Risk of ischemic heart

disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; *368* : 987-98.

51. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: Pathologic abnormalities and putative mechanisms. *Front Oncol* 2015; *5* : 39.

52. Wennstig AK, Garmo H, Isacsson U, Gagliardi G, Rintelä N, Lagerqvist B, *et al*. The relationship between radiation doses to coronary arteries and location of coronary stenosis requiring intervention in breast cancer survivors. *Radiat Oncol* 2019; *14* : 40.

53. Drost L, Yee C, Lam H, Zhang L, Wronski M, McCann C, *et al*. A systematic review of heart dose in breast radiotherapy. *Clin Breast Cancer* 2018; *18* : e819-24.

54. Desai N, Currey A, Kelly T, Bergom C. Nationwide trends in heart-sparing techniques utilized in radiation therapy for breast cancer. *Adv Radiat Oncol* 2019; *4* : 246-52.

55. Smyth LM, Knight KA, Aarons YK, Wasiak J. The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: A systematic review. *J Med Radiat Sci* 2015; *62* : 66-73.

56. Prabhakar R, Tharmar G, Julka PK, Rath GK, Joshi RC, Bansal AK, *et al*. Impact of different breathing conditions on the dose to surrounding normal structures in tangential field breast radiotherapy. *J Med Phys* 2007; *32* : 24-8.

57. Swamy ST, Radha CA, Kathirvel M, Arun G, Subramanian S. Feasibility study of deep inspiration breath-hold based volumetric modulated arc therapy for locally advanced left sided breast cancer patients. *Asian Pac J Cancer Prev* 2014; *15* : 9033-8.

58. Sripathi LK, Ahlawat P, Simson DK, Khadanga CR, Kamarsu L, Surana SK, *et al*. Cardiac dose reduction with deep-inspiratory breath hold technique of radiotherapy for left-sided breast cancer. *J Med Phys* 2017; *42* : 123-7.

59. Kunheri B, Kotne S, Nair SS, Makuny D. A dosimetric analysis of cardiac dose with or without active breath coordinator moderate deep inspiratory breath hold in left sided breast cancer radiotherapy. *J Cancer Res Ther* 2017; *13* : 56-61.

60. Chatterjee S, Chakraborty S, Moses A, Nallathambi C, Mahata A, Mandal S, *et al*. Resource requirements and reduction in cardiac mortality from deep inspiration breath hold (DIBH) radiation therapy for left sided breast cancer patients: A prospective service development analysis. *Pract Radiat Oncol* 2018; *8* : 382-7.

61. Rafic KM, Patricia S, Timothy Peace B, Sujith CJ, Selvamani B, Ravindran PB. Dosimetric and clinical advantages of adapting the DIBH technique to hybrid solitary dynamic portal radiotherapy for left-sided chest-wall plus regional nodal irradiation. *Med Dosim* 2020; *45* : 256-63.

62. Misra S, Mishra A, Lal P, Srivastava R, Verma M, Senthil Kumar SK, *et al*. Cardiac dose reduction using deep inspiratory breath hold (DIBH) in radiation treatment of left sided breast cancer patients with breast conservation surgery and modified radical mastectomy. *J Med Imaging Radiat Sci* 2021; *52* : 57-67.

63. Ferdinand S, Mondal M, Mallik S, Goswami J, Das S, Manir KS, *et al*. Dosimetric analysis of deep inspiratory breath-hold technique (DIBH) in left-sided breast cancer radiotherapy and evaluation of pre-treatment predictors of cardiac doses for guiding patient selection for DIBH. *Tech Innov Patient Support Radiat Oncol* 2021; *17* : 25-31.

64. Simonetto C, Eidemüller M, Gaasch A, Pazos M, Schönecker S, Reitz D, *et al*. Does deep inspiration breath-hold prolong life? Individual risk estimates of ischaemic heart disease after breast cancer radiotherapy. *Radiother Oncol* 2019; *131* : 202-7.

65. Nattinger AB, Gottlieb MS, Veum J, Yahnke D, Goodwin JS. Geographic variation in the use of breast-conserving treatment for breast cancer. *N Engl J Med* 1992; *326* : 1102-7.

66. Hiotis K, Ye W, Sposto R, Skinner KA. Predictors of breast conservation therapy: Size is not all that matters. *Cancer* 2005; *103* : 892-9.

67. Fowble B, Solin LJ, Schultz DJ, Goodman RL. Frequency, sites of relapse, and outcome of regional node failures following conservative surgery and radiation for early breast cancer. *Int J Radiat Oncol Biol Phys* 1989; *17* : 703-10.

68. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, *et al*. Radiotherapy after breast-conserving surgery in small breast carcinoma: Long-term results of a randomized trial. *Ann Oncol* 2001; *12* : 997-1003.

69. Marta GN, Barrett J, Porfirio GJ, Martimbianco AL, Bevilacqua JL, Poortmans P, *et al*. Effectiveness of different accelerated partial breast irradiation techniques for the treatment of breast cancer patients: Systematic review using indirect comparisons of randomized clinical trials. *Rep Pract Oncol Radiother* 2019; *24* : 165-74.

70. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, *et al*. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017; *390* : 1048-60.

71. Shah C, Badiyan S, Ben Wilkinson J, Vicini F, Beitsch P, Keisch M, *et al*. Treatment efficacy with accelerated partial breast irradiation (APBI): Final analysis of the American Society of Breast Surgeons MammoSite(®) breast brachytherapy registry trial. *Ann Surg Oncol* 2013; *20* : 3279-85.

72. Polgár C, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, *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 and *in-situ* carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2017; *18* : 259-68.

73. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, *et al*. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. *Lancet Oncol* 2013; *14* : 1269-77.

74. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, *et al*. Risk-adapted targeted intraoperative

radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; *383* : 603-13.

75. Hickey BE, Lehman M, Francis DP, See AM. Partial breast irradiation for early breast cancer. *Cochrane Database Syst Rev* 2016; *7* : CD007077.

76. Korzets Y, Fyles A, Shepshelovich D, Amir E, Goldvaser H. Toxicity and clinical outcomes of partial breast irradiation compared to whole breast irradiation for early-stage breast cancer: A systematic review and meta-analysis. *Breast Cancer Res Treat* 2019; *175* : 531-45.

77. Wadasadawala T, Budrukkar A, Chopra S, Badwe R, Hawaldar R, Parmar V, *et al*. Quality of life after accelerated partial breast irradiation in early breast cancer: Matched pair analysis with protracted whole breast radiotherapy. *Clin Oncol* 2009; *21* : 668-75.

78. Wadasadawala T, Sinha S, Parmar V, Verma S, Gaikar M, Kannan S, *et al*. Comparison of subjective, objective and patient-reported cosmetic outcomes between accelerated partial breast irradiation and whole breast radiotherapy: A prospective propensity score-matched pair analysis. *Breast Cancer* 2020; *27* : 206-17.

79. Budrukkar A, Telkhade T, Wadasadawala T, Shet T, Upreti RR, Jalali R, *et al*. A comparison of long-term clinical outcomes of accelerated partial breast irradiation using interstitial brachytherapy as per GEC-ESTRO, ASTRO, updated ASTRO, and ABS guidelines. *Brachytherapy* 2020; *19* : 337-47.

80. Budrukkar A, Gurram L, Upreti RR, Munshi A, Jalali R, Badwe R, *et al*. Clinical outcomes of prospectively treated 140 women with early stage breast cancer using accelerated partial breast irradiation with 3 dimensional computerized tomography based brachytherapy. *Radiother Oncol* 2015; *115* : 349-54.

81. Kumar R, Sharma SC, Kapoor R, Singh R, Bhardawaj A. Dosimetric evaluation of 3D conformal accelerated partial-breast irradiation vs. whole-breast irradiation: A comparative study. *Int J Appl Basic Med Res* 2012; *2* : 52-7.

82. Yoon JJ, Green WR, Kim S, Kearney T, Haffty BG, Eladoumikdachi F, *et al*. Oncoplastic breast surgery in the setting of breast-conserving therapy: A systematic review. *Adv Radiat Oncol* 2016; *1* : 205-15.

83. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, *et al*. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol* 2013; *31* : 2382-7.

84. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II Investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): A randomised controlled trial. *Lancet Oncol* 2015; *16* : 266-73.

85. Tang L, Matsushita H, Jingu K. Controversial issues in radiotherapy after breast-conserving surgery for early breast cancer in older patients: A systematic review. *J Radiat Res* 2018; *59* : 789-93.

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