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COMPARISON OF THE TWO MOST COMMONLY USED DOSE FRACTIONATION REGIMENS FOR EXTERNAL BEAM APBI: A LITERATURE REVIEW

Oncology/Radiotherapy

Dr. Vrushab Rao* MBBS, Department of Cyberknife Radiosurgery and Radiation Oncology Ruby Hall Clinic, 40, Sassoon Road, Pune – 411001, Maharashtra, India *Corresponding Author

Dr. Soumya Singh MBBS

Dr. Bhooshan Zade MD, DNB, PDCR

ABSTRACT

APBI is an accepted treatment modality for early-stage breast cancer. Various modalities have been used to deliver APBI and external beam radiation is a feasible option. Being non-invasive and having a short treatment time, it has better patient compliance. Various dose fractionation regimens have been used for APBI among which two are used commonly - 38.5 Gy in 10 fractions delivered twice a day and 30 Gy in 5 fractions delivered once a day. Here we study the results of existing literature on the fractionation regimens and compare the outcomes to ascertain the better of the two them.

KEYWORDS

INTRODUCTION-

Breast cancer still ranks as the most common cancer in women across the world. The occurrence of breast cancer has shown an upward trend over the majority of the last forty years. In the latest available data spanning from 2010 to 2019, there was an annual increase in the rate, predominantly influenced by cases of localized-stage and hormone receptor-positive breast cancer.[1] According to the GLOBOCAN database, 2.3 million women were diagnosed with breast cancer, and 685,000 fatalities were due to the disease directly. 3 million new cases and 1 million deaths yearly are estimated by 2040.[2] It also accounted for 28.8% of cases of all cancers detected in women in India making it the single largest cause of cancer in the country.[3] With the burden of the disease set to rise in the coming years, finding treatment alternatives that preserve cosmesis and quality of life while ensuring disease-free survival is of paramount importance and has been an avenue of research.

The treatment of breast cancer has always been a multi-disciplinary approach.

The standard treatment for women with early-stage breast cancer has been breast-conserving surgery combined with whole-breast irradiation (WBI) (Figure 1), which can produce cancer results similar to mastectomy.[4] In the era of hypofractionated radiotherapy, the low α/β ratio of breast tumors makes these tumors permissible to receive a high dose per fraction to an equivalent dose of around 50 Gy. Hypofractionated regimens in breast cancers have shown equal efficacy in WBI.[5][6]

Patterns of recurrence showed that most cases of recurrent breast cancer in breast conservation surgery occurred around the lumpectomy cavity. [7] Large treatment volumes in whole breast irradiation (WBI) and prolonged treatment durations can be costlier, less comfortable, and risk delivering increased doses to the critical structures around.[8][9] Consequently, Accelerated Partial Breast Irradiation (APBI) was devised to diminish the treated area's size and shorten the overall treatment time (Figure 2). APBI through external beam radiotherapy (EBRT) in early breast cancer cases is non-inferior to whole breast irradiation [10] and provides an additional benefit over brachytherapy or intraoperative radiotherapy (IORT) of being non-invasive as it uses 3-D conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) like conventional WBI.

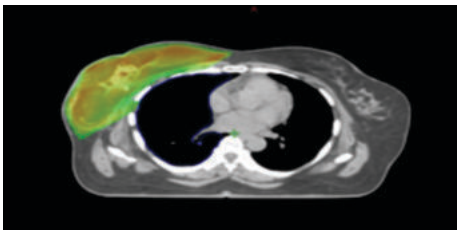


Figure 1 - Whole breast irradation.

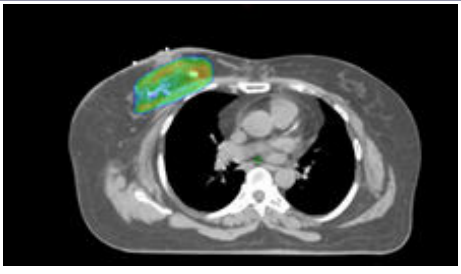


Figure 2 - Partial breast irradiation.

Over the years, various fractionation regimens for APBI have been reported with favorable outcomes [11] where hypofractionation has been used to reduce the treatment time and volume, though two protocols are used commonly presently - 30 Gy in 5 fractions once daily and 38.5 Gy in 10 fractions twice daily. In this literature review, we present the data available on the two regimens and assess their effects and outcomes.

The rationale for APBI -

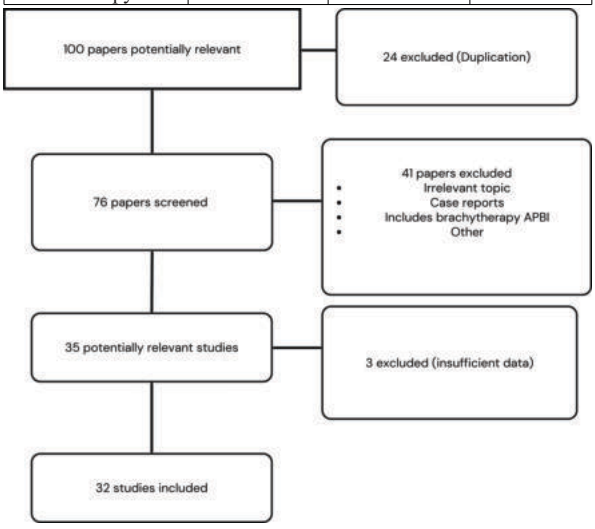
The SEER data showed that around 60% of all breast cancers are diagnosed in the early stages.[12] It was also found in re-excision specimens that only 9% had residual disease that extended beyond 15 mm of the initial excision cavity, and over 90% of the cases with negative margins did not have any residual disease beyond 10mm. [13] In addition, 40% of WBI patients had dermatitis [8], and the maximum physician-reported acute dermatitis was 36% in hypofractionated WBI and 69% in conventional WBI.[14] This paved the way for partial breast irradiation in selected cases which could limit the treatment volume while reducing acute and late toxicities. With a low α/β ratio, breast tumors could be treated with a high dose per fraction. This led to the practice being studied at the start of this century and is now an accepted treatment modality. The technique was initially used for brachytherapy and intraoperative radiotherapy but now it is used with EBRT as well.

Patient Selection for APBI -

Table 1 describes the ASTRO 2017 consensus guidelines for APBI.[15]

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



Selection of literature -

Two independent reviewers were involved in the data selection. A bibliographical search was performed of PubMed, Embase, and Google Scholar for eligible studies. The main keywords used for the search were 'APBI', 'accelerated partial breast irradiation', 'breast cancer', '30 Gy in 5 fractions', and '38.5 Gy in 10 fractions'. Only studies published in the English Language were included. Relevant data was retrieved from the selected studies.

Comparing 2 Dose Fractionation Regimens -

Various dose fractionation regimens have been tested in a clinical setting and their findings published.[16][17][18] However, two APBI dose regimens are used extensively in today's practice - 38.5 Gy in 10 fractions delivered as 2 fractions per day, and 30 Gy in 5 fractions delivered once a day. The overall treatment time for both of them is 5 days, and the equivalent dose at 2 Gy per fraction is 52.75 Gy and 54 Gy respectively which is almost equivalent to the dose prescribed in whole breast irradiation. Studies have been published on both protocols, however, there are no detailed comparative researches published to date. We discuss them in more depth below, exhibiting their significance through a detailed review of existing literature.

1. 38.5 Gy in 10 fractions

Data on 38.5 Gy in 10 fractions exists from the past two decades. Initial studies commented mostly on the cosmetic outcomes and the later publications commented on disease and survival outcomes. Baglan et al.[19] and Vicini et al.[20] were one of the first to comment on the cosmetic outcomes and dosimetry of using 3DCRT to deliver 38.5 Gy in 10 fractions twice a day. No grade 3 toxicities were observed in both studies and all evaluated patients till 8 weeks and 2 years respectively had good/excellent cosmetic outcomes. A subsequent study on the cosmesis with 2-4 year results confirmed the findings of the previous studies.[21] All grade I and II toxicities resolved within 3 years and only 2 patients developed pain (grade III), and no local recurrences were reported.

The National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413 protocol (NSABP B-39/RTOG 041)[22] and the NRG Oncology RTOG 0319[23][24] were 2 trials conducted to study the efficacy of 38.5 Gy in 10 fractions using 3DCRT. While no treatment deaths were reported in the NSABP B-39/RTOG 041, the ipsilateral breast tumor recurrence (IBTR) was 4.6% in the APBI arm compared to 3.9% in the WBI arm, with a difference of <1%. 2% of patients in both arms died of recurrent breast cancer. Toxicities in the APBI vs. WBI arm were - grade I 40% vs 31%, grade 2 44% vs 31%, and grade 3 in 10% vs 7%. However, the trial did not meet the criteria for equivalence to whole-breast irradiation in controlling IBTR. The initial results of NRG Oncology RTOG 0319 showed an ipsilateral breast failure (IBF), ipsilateral nodal failure (IBF), contralateral breast failure (CBF), distant failure (DF), mastectomy-free survival (MFS), disease-free survival (DFS), and overall survival (OS) rates of 6%, 2%, 8%, 90%, 84%, and 96% respectively. In the long-term results, however, the 7-year estimates of all IBRs, INR, mastectomy rate, distant metastasis, MFS, DFS, and OS were 7.7%, 5.8%, 7.7%, 7.7%, 71.2%, 71.2%, and 78.8% respectively. 3 patients died of breast cancer and 4 patients had Grade III toxicities. The overall results are promising in terms of tumor control and toxicities. These results were of phase I and II trial and phase III trial results are awaited. The IRMA trial is the latest randomized control trial with published results.[26][27] While the initial results showed comparable physician-related outcomes (20% vs. 21.8% 1 year, 20% vs 19% 3 years) and grade 3 acute and late toxicities (0 vs 1.4% and 0.42% vs 0.79% respectively) in the APBI vs WBI arms, the final results showed a significant difference with worse outcomes in the APBI arm as compared to WBI arm in terms of skin toxicities at 3 and 5 years (12.7% v 9.2% and 14% v 9.8%), and grade III or more late soft tissue toxicity and bone side effects (3.2% vs 1% and 1.1% vs 0%). Overall toxicities were comparable in both arms.

The RAPID trial reported IBTR of 3·5% vs. 2·6%, regional recurrence of 0·4% vs. 0·2%, and distant recurrence of 1·9% vs. 1·7% in the APBI vs. WBI arms. Acute toxicities in the two arms respectively corresponded to 28% vs. 45.4% and late toxicities were 32.3% vs. 13.3%. Nurses' assessment of cosmetic outcomes was fair or poor in 36% of patients who received APBI and in 19% of patients who received WBI. [10]

Cosmetic outcomes using 3DCRT were the aim of studies by Chen et al., Gatti et al., Shah et al., and Hepel et al.[28][29][30][31] The first three studies showed that APBI had excellent to good cosmesis in over 80% of the patients and in addition, the study by Chen et al. had good efficacy rates with an IBF of 1.1%, INF of 0%, DF of 3.9% DFS of 95% and OS of 97%, Hepel et al., who used the NSABP B-39/RTOG 041 protocol, found that 10% of patients who received 38.5 Gy in 10 fractions developed moderate-to-severe late toxicity within 15 months. Subcutaneous fibrosis was the most common adverse effect noted.

While most studies use 3DCRT, a few publications have used IMRT to deliver APBI. The APBIMRT trial reported an IBTR of 0.7 %, CBF of 0 %; distant failure of 0.9 %, OS of 96.8 %, cancer-specific survival (BCSS) of 100 %, and physicians rated cosmesis as excellent/good in 88.2 and 90.5 %.[32] With the use of IMRT and other motion management techniques such as DIBH, the constraints set for APBI using IMRT can be stricter as V50 and V100 corresponded to the adverse cosmetic outcomes.[33]

1. 30 Gy in 5 fractions

Studies on 5 fraction APBI were published as early as 2002 in the USC Feasibility Pilot Study with promising results.[34] 30 Gy in 5 fractions has been extensively studied thereafter and various delivery techniques, stated subsequently, have been used to treat breast cancer.

The groundbreaking trial for 30 Gy in 5 fractions was the APBI-IMRT-Florence Trial.[35] The study compared 5 fraction WBI plus boost with APBI and noted the 5-year difference in IBTR, OS, BCSS at 10 years and acute and late toxicities. APBI, here, was delivered using IMRT. While the IBTR, OS, and BCSS rates were similar in both arms (2.5% vs. 3.7%, 91.9% vs. 91.9%, and 96.7% vs. 97.8% respectively for WBI and APBI), the APBI arm showed less acute and late toxicities, and better patient and physician reported cosmetic outcomes. The findings corroborated their 5-year results as well.[36]

3DCRT has been used in the prone position to treat early-stage breast cancers. The NYU 00-23 by Formenti et al. studied prone position APBI using 3DCRT.[37][38] The V100 was 26% in the initial results and only grade I acute and late toxicities were reported in the patients who were followed up for a median of 18 months. In the long-term results, the DFS was 95%, IBF was 1%, CBF was 1%, DF was 1%, and only 2% of the patients had grade 2 and grade 3 toxicities each. Cosmesis was good and excellent in 42% and 47% of the patients respectively. The 1 to 1.5cm margin generally covers the setup errors. Shah et al. reported an IBTR of 2.1%, CBF of 2.7%, 0.3% DF, DFS of 96.7%, and OS of 98.1% when patients were treated with APBI using 3DCRT in the prone position. [39]The reproducibility of the prone position was reported by NYU 07-582 and a recommended margin of

1.26, 0.73, and 0.96 cm in the anteroposterior, superoinferior, and mediolateral directions was concluded. [40]

Wen et al. studied whether prone APBI complied with the RTOG-0413 while using the contouring guidelines suggested by 00-23 and 07-582 protocols.[41] 2 trials were conducted - one with 3DCRT and one with image-guided radiation therapy/intensity-modulated radiation therapy (IGIMRT). While most of the criteria were met, the dose to the contralateral breast was higher due to the difference in contouring patterns and slightly larger margins.

The dose fractionation has also been studied using volumetric modulated arc therapy (VMAT) and stereotactic body radiotherapy (SBRT). Using VMAT, only 1.3% of the patients had grade II fibrosis and all other acute adverse events were grade 0 or grade I.[42] Using SBRT, over 95% of the patients had grade I acute toxicities and all the patients had good to excellent cosmesis.[43][44] One nodal failure and one IBTR were reported in the two studies respectively.

Better fractionation regimen and future directions

Based on the available literature, 30 Gy in 5 fractions has favorable and promising outcomes in all the studied parameters. The failures with 38.5 Gy in 10 fractions in terms of recurrences and late toxicities as compared to whole breast irradiation determined by large randomized control trials is a disadvantage. The results are comparable in the other parameters.

However, most of the studies reported using 30 Gy in 5 fractions have a smaller sample size as compared to the studies using 38.5 Gy in 10 fractions. In addition, the number of randomized trials is fewer with the 5-fraction APBI and requires further investigation with a larger population. The data collected over various studies differed in the parameters tested and trials with uniform study designs are needed.

Going ahead, the results of NCT02375048, NCT02272400, and NCT02637024 would aid in confirming the analysis of this literature review.[45][46][47]

A meta-analysis of the available literature and randomized control trials comparing the two fractionation regimens would yield the results needed to unravel the dose dilemma.

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