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MANAGEMENT AND OUTCOME OF RADIOTHERAPY FOR BREAST CANCER : A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: A key component of breast cancer treatment is breast irradiation therapy, which provides the best control and precision. Fractionated whole-breast irradiation, or WBI, is the recommended approach for best outcomes. The goal of this study is to conduct a thorough evaluation of the literature from the previous ten years about the administration and results of radiation therapy for breast cancer. **Methods:** Using the PRISMA 2020 principles, this systematic review concentrated on full-text English literature that was published between 2014 and 2024. Submissions without a DOI, editorials, and review papers from the same publication were not taken into consideration. Online resources like ScienceDirect, SagePub, and PubMed were used to compile the literature. **Result:** More than 100,000 papers were first obtained by our research team from reliable sources like Science Direct, PubMed, and SagePub. Only six publications were found to be directly relevant to our ongoing systematic review using a rigorous three-level screening approach. These articles were then chosen for additional examination by in-depth full-text reading. **Conclusion:** An essential component of breast cancer treatment is adjuvant radiation, which eliminates any remaining cancer in the surgery room and surrounding satellites. Shorter courses are preferred for patients with localized breast cancer to preserve early-stage illness and manage tumors.

Keyword: *breast cancer, irradiation, therapy, WBI*

INTRODUCTION

Breast-conserving therapy (BCT) is the recommended course of treatment for the majority of patients with early-stage breast cancer (BC).[1] It entails a partial mastectomy followed by breast irradiation.[2] For some older (75 years) patients with breast cancer who are at low risk of recurrence, skipping radiation therapy may be an option, but in most cases, this practice increases ipsilateral breast tumor recurrence (IBTR), which in certain cases is linked to a higher breast cancer death than in patients with the recurrence-free disease.[3] When compared to mastectomy, BCT is linked to better patient sexual function, body image, and quality of life (QoL).[4] According to randomized trials, the incidence of breast tumor recurrence is about halved when whole-breast radiation is administered after breast-conserving surgery, with or without a tumor-bed boost.[5]

For many years, the traditional procedure for fractionated whole-breast irradiation (WBI) involved time-consuming patients, typically requiring 5-7 weeks, and could involve an additional tumor bed dose.[2] In the past, 50 Gy of radiation treatment was given in 25 portions over 5 weeks as the usual treatment for breast cancer. Here, the dose per fraction is 2 Gy; this is referred to as conventional fractionation. A boost dosage of 10–20 Gy in 5–10 portions given over 5–10 days is sometimes given to younger patients and those with high-risk diseases after this, extending the treatment period to 6–7 weeks, which is a lengthy period. High doses per fraction given over a shorter period are known as hypofractionation.[6] Extensive phase III experiments have demonstrated that hypofractionated WBI can shorten total irradiation times without sacrificing local control or compromising safety.[2] In the UK and a few Canadian locations, hypofractionation is also a common procedure.[7] Results from research utilizing ultra hypofractionated (UHF) WBI in conjunction with BCT have been published more recently. For women with early-stage breast cancer, the FAST study compared 50 Gy in 25 fractions to 28.5 or 30 Gy in 5 once-weekly fractions.[8]

In certain low-risk early breast cancer patients, partial-breast irradiation (PBI) has been proposed as an alternate strategy for adjuvant radiotherapy (RT) following partial mastectomy. Improved safety profile, potential cost savings, and a shorter overall treatment duration when RT is accelerated (APBI, accelerated partial breast irradiation) are projected benefits of PBI over WBI.[1] The American Society for Radiation Oncology and the Groupe Européen de Curiethérapie/European Society for Radiotherapy Oncology have both produced recommendations for APBI.[9,10] However, an increased risk of late normal tissue harm, including an approximate doubling of breast fibrosis, which increases with irradiation volume, offsets the potential local control improvement with boost. Boost is typically given in 5–8 treatments (fractions) consecutively following whole-breast radiation, which increases the treatment load on patients and healthcare systems.[5]

As of right now, 40–42.5 Gy is administered in 15–16 fractions over three weeks as the standard for hypofractionation in breast cancer. This is followed by a boost of 10–16 Gy in 5–8 fractions over two weeks.[6] In breast cancer, accelerated hypofractionation (34 Gy given in 10 fractions over 2 weeks) provides a further option.[7] A higher radiation dose per fraction, target-specific targeting, and a reduction in the exposure to surrounding normal tissues are the reasons why APBI, which is based on the concepts of hypofractionation, is faster and less intrusive. Additionally, it enhances the precision of treatment by utilizing various machine devices currently in use, like image-guided radiotherapy (IGRT) directed at tumor bed clips using CT devices on the linear accelerator platform (cone beam computed tomography, or CBCT) irradiation in deep inspiration breath hold (DIBH technique) to halt breast movements during breathing; rapid and precise dosing administration using radiation beams without a homogenizing filter at a high dose rate (flattening filter free beams, or FFF); or patient positioning correction with a six-degree-of-fingerchair (6DoF couch).[1,11] Ten-year results demonstrated that 28.5 Gy was similar to conventional fractionation in terms of detrimental effects on the breast. Five-year results showed that, in terms of expected tissue effects and local control, 26 Gy in 5 fractions was not inferior to 40 Gy in 15 fractions.[12]

This study aims to provide a comprehensive review of the literature covering the previous ten years about the management and results of radiation therapy for breast cancer.

METHODS

Protocol

The author of the work complied strictly with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Ensuring the study satiated all of the requirements was the aim of this. The selected methodology was deliberately crafted to guarantee the precision and reliability of the inquiry's conclusions.

Criteria for Eligibility

This study does a comprehensive assessment of the literature over the past ten years regarding the management and outcome of radiotherapy for breast cancer. By carefully examining data, this study aims to shed light on patient treatment methods and make improvements. This paper's main objective is to draw attention to the importance of the important issues that have been found in the literature overall.

Strict inclusion and exclusion criteria are used in this study to guarantee the caliber of the included material. To be eligible for inclusion, papers have to be published between 2014 and 2024 in the English language. Editorials, submissions without a DOI, already published review pieces, and duplicate journal entries are among the exclusion criteria.

Search Strategy

The keywords used for this research is "management and outrome of radiotherapy for breast cancer". The Boolean MeSH keywords inputted on databases for this research are: *((("Breast cancer"[MeSH Terms] OR ("breast cancer"[All Fields] AND "radiotherapy"[All Fields]) OR ("radiotherapy"[MeSH Terms] OR ("radiology"[All Fields] AND "therapy"[All Fields]) AND ("management"[MeSH Terms] OR "management"[All Fields] OR "outcome"[All Fields] OR "outcome"[MeSH Subheading] OR "result"[All Fields] OR "prognosis"[All Fields]))))*

Data retrieval

To determine the relevance of each paper, the authors carefully considered its abstract and title before conducting this systematic review. For additional review, only publications that satisfied the inclusion requirements and related to the goals of the article were chosen. A consistent pattern discovered over multiple examinations ultimately produced a conclusive result. The chosen contributions had to be full-text and in English. The most rigorous screening process was used to include content that met all predetermined inclusion criteria and had a direct bearing on the subject of the study. Research that did not meet these standards was routinely disregarded, and their findings were not taken into account. Numerous details found during the research process, including titles, authors, publication dates, locations, study techniques, and parameters, were examined in detail during a detailed examination.

Quality Assessment and Data Synthesis

To ascertain which publications required more research, the authors separately reviewed the research presented in the titles and abstracts of each publication. The next step involved going over each document that met the predetermined standards for being included in the review. The evaluation procedure yielded findings that informed the decision to include an article in the review. This criterion achieved the goal of expediting the process of selecting papers for additional assessment, enabling an in-depth examination of earlier studies and the elements that made them eligible for the review.

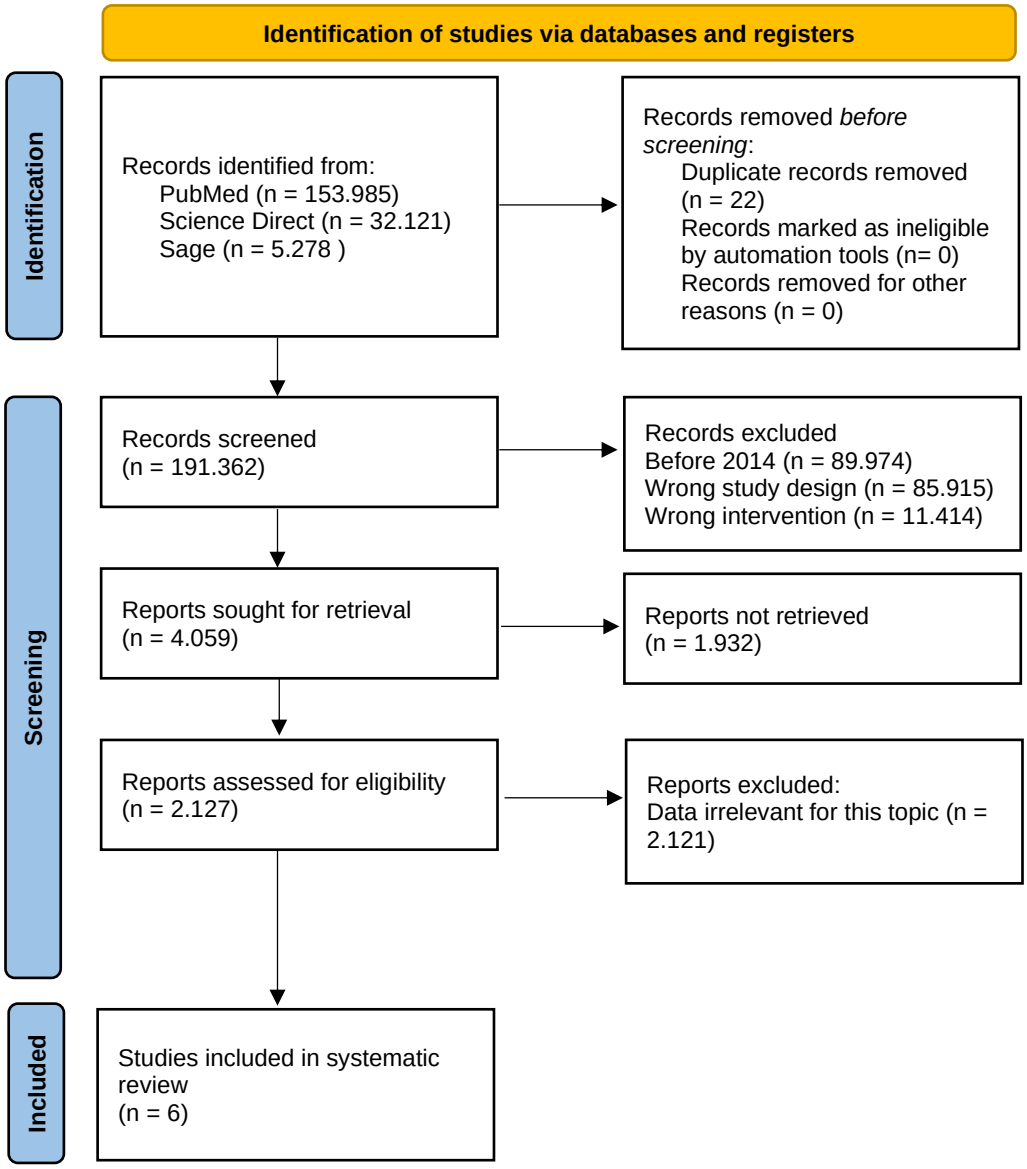

Figure 1. Article search flow chart

RESULT

Our research team first collected more than 100,000 publications from reliable sources like Science Direct, PubMed, and SagePub. Only six papers were found to be directly relevant to our ongoing systematic review following a rigorous three-level screening approach. These publications were then chosen for in-depth full-text reading and additional analysis. The literature that was examined for this analysis has been gathered in Table 1 for simplicity of presentation.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Coles et al.[13] (2017)	Multicenter	Randomized Controlled Trial	2.016 patients	2.016 women were enlisted. The use of two women's data in the analysis was discontinued with their consent. The whole-breast irradiation (control) group included 674 patients, the reduced-dose group included 673 patients, and the partial-breast group included 669 patients. A 5-year estimate of the cumulative incidence of local relapse was 1·1% for patients in the control group, 0·2% for those in the reduced-dose group, and 0·5% for those in the partial-breast group. The median follow-up was 72·2 months. For the reduced-dose and partial-breast groups, the estimated 5-year absolute differences in local relapse relative to the control group were –0·73% and –0·38%, respectively. It is possible to assert non-inferiority for both partial-breast and reduced-dose radiation therapy. This was validated by testing against the critical HR above 2·03 (p=0·003 for the partial-breast group and p=0·016 for the reduced-dose group, in comparison to the whole-breast radiation group).
Vicini et al.[3] (2019)	Multicenter	Randomized Controlled Trial	4.216 patients	4.216 women were enrolled at the beginning. 2107 people were placed in the accelerated partial breast irradiation (APBI) group and 2109 in the whole-breast irradiation group. Ultimately, 2089 patients in the APBI group and 2036 patients in the whole-breast irradiation group were eligible to be evaluated for the primary outcome. 90 (4%) of 2089 women eligible for the primary outcome in the APBI group and 71 (3%) of 2036 women in the whole-breast irradiation group experienced ipsilateral breast tumor recurrence (IBTR) after a median follow-up of 10·2 years. In the APBI group, the 10-year cumulative incidence of IBTR was 4·6%, while in the whole-breast irradiation group, it was 3·9%. Recurrent breast cancer claimed the lives of 44 (2%) of 2039 patients in the group receiving whole-breast irradiation and 49 (2%) of 2093 patients in the APBI group.
Brunt et al.[8] (2020)	Multicenter	Randomized Controlled Trial	4.096 patients	4096 patients from 97 UK centers were recruited, and with their consent, we were able to get treatment plans for 1361 of them (the 40 Gy schedule, 1367 for the 27 Gy schedule, and 1368 for the 26 Gy schedule). 79 patients (31 in the 40 Gy group, 27 in the 27 Gy group, and 21 in the 26 Gy group) experienced the primary endpoint event at a median follow-up of 71·5 months; HRs versus 40 Gy in 15 fractions were 0·86 for 27 Gy in five fractions and 0·67 for 26 Gy in five fractions. The calculated absolute differences vs 40 Gy in 15 fractions were –0·3% for 27 Gy in five fractions and –0·7% for 26 Gy in five fractions. The 5-year

				incidence of ipsilateral breast cancer return following 40 Gy was 2·1%.
Coles et al.[5] (2023)	Multicenter	Randomized Controlled Trial	2.617 patients	A total of 2617 patients were enrolled. 871 people were divided into three groups: the control group (871), test group 1 (874), and test group 2 (872). 13 cm^3 was the median enhanced clinical goal volume. There were 76 IBTR events at a median follow-up of 74 months (20 for test group 1, 21 for test group 2, and 35 for test group 2). The control group's 5-year IBTR incidence was 1.9%, test group 1's was 2.0%, and test group 2's was 3.2%. For test groups 1 and 2, the estimated absolute differences compared to the control group were 0·1% and 1·4%, respectively. For 48 Gy, the upper confidence limit for test group 1 compared to the control group showed non-inferiority. Over 5 years, the control group experienced a cumulative 5-year incidence of 11·5% of clinician-reported moderate or marked breast induration, test group 1 experienced 10·6% (p=0·40 vs control group), and test group 2 experienced 15·5% (p=0·015 vs control group).
Laughlin et al.[12] (2023)	Multicenter	Randomized Controlled Trial	107 patients	One hundred seven patients were randomly assigned to receive adjuvant whole breast irradiation (WBI) by either ultra hypofractionation (UHF) (n = 53) or moderate hypofractionation (MHF) (n = 54). 42.8 months was the median follow-up period. At the end of treatment (EOT), 4 patients (7.4% in the MHF arm and 2 patients (3.7%) in the UHF arm had grade 2 radiation dermatitis. There were no toxicities detected at grade 3 or above. At EOT, 2 (6.7%) patients treated in the UHF arm and 1 (1.9%) patient treated in the MHF arm showed deterioration of cosmesis by physician assessment; however, at 3 months, only 1 (1.8%) patient treated in the MHF arm showed deterioration of cosmesis. 91% and 94% of patients treated with MHF and UHF regimens, respectively, reported excellent/good cosmesis at EOT. When compared to patients in the UHF arm, more patients in the MHF arm (100% vs. 91%; P =.030) reported excellent/good cosmesis at three months. However, at the 1-, 2-, and 3-year intervals, the variation in the patient-reported cosmesis vanished.
Burkon et al.[1] (2024)	Chezcia	Randomized Controlled Trial	84 patients	Over a median follow-up of 37 months (range 21–45 months), the analysis of 84 patients with a median age of 64 years revealed significantly fewer acute adverse events in the accelerated partial breast irradiation (APBI) arm, related skin responses, and local, and general symptoms. Regarding grade ≥ 2 late skin toxicity, there was a statistically significant difference favoring the APBI arm (p = 0.026). In the WBI and APBI arms, late toxicity (deformation, edema, fibrosis, and discomfort) in the breast area affected the patient's quality of life and appearance.

				This occurred in 61% and 17% of patients, respectively. In the APBI arm, the cosmetic outcome was better, particularly six to twelve months after the radiation.

According to a 2017 study by Coles et al., involving 2.016 women included a control group, a reduced-dose group, and a partial-breast group. The cumulative incidence of local relapse was 1·1% for the control group, 0·2% for the reduced-dose group, and 0·5% for the partial-breast group. The median follow-up was 72·2 months. The partial-breast group showed non-inferiority in local relapse compared to the control group. Adverse effects from reduced-dose or partial-breast radiation were similar, but two patient domains showed statistically significantly fewer adverse effects. The study concluded that both partial-breast and reduced-dose radiation therapy are effective in treating breast cancer.[13]

In a trial intervention conducted by Vicini et al. 2019, the accelerated partial breast irradiation (APBI) group and whole-breast irradiation groups were evaluated for the primary outcome of ipsilateral breast tumor recurrence (IBTR). The APBI group experienced a 10-year cumulative incidence of IBTR of 4·6%, while the whole-breast irradiation group had a 3·9% incidence. Recurrent breast cancer claimed the lives of 22% of 2039 patients in the whole-breast irradiation group and 22% of 2093 patients in the APBI group. No deaths were attributed to the treatment, and the two groups had comparable rates of treatment-related toxicities and secondary malignancies. The APBI group had the highest reported toxicity grade, while the whole-breast irradiation group had the lowest.[3]

A study conducted by Brunt et al. in 2020 examined the treatment plans that were developed for 4096 UK patients, with 1361 receiving the 40 Gy, 27 Gy, and 26 Gy schedules. The primary endpoint event occurred in 79 patients, with HRs varying between 0·86 and 0·67 for each group. The 5-year incidence of ipsilateral breast cancer return following 40 Gy was 2·1%. Five years later, 98 of 986 40 Gy patients, 155 of 1005 27 Gy patients, and 121 of 1020 26 Gy patients had moderate or significant normal tissue effects.[8]

The study by Coles et al. in 2023 found that the study involved 2617 patients divided into three groups: control group (871), test group 1 (874), and test group 2 (874). The median enhanced clinical goal volume was 13 cm^3. Over 5 years, the control group experienced a cumulative 5-year incidence of 11·5% of clinician-reported moderate or marked breast induration, while the test group experienced 10·6% and 15·5%, respectively.[5]

According to Laughlin et al. 2023, The study compared patients treated with ultra hypofractionation (UHF) and moderate hypofractionation (MHF) for adjuvant whole-breast irradiation. At the end of treatment (EOT), 7.4% in the MHF arm and 3.7% in the UHF arm had grade 2 radiation dermatitis. At 3 months, only 1.8% in the MHF arm showed deterioration of cosmesis. Both regimens reported excellent/good cosmesis at EOT.[12]

According to the Burkon et al. trial, at a median follow-up of 37 months, the APBI arm experienced fewer adverse events, including fewer skin responses and symptoms. The patient's appearance and quality of life were negatively impacted by the statistically significant difference in late skin toxicity observed in the APBI arm. In the APBI arm, especially six to twelve months following radiation, the cosmetic result was superior.[1]

DISCUSSION

According to a study conducted by Coles et al. in 2017, the results at the 5-year mark confirm that non-inferiority was demonstrated for both reduced-dose and partial-breast irradiation. Local relapse was rare in both trial groups, and late normal-tissue effects were rare across all groups. The partial-breast irradiation group had a lower incidence of breast hardness compared to the control group.[13] Brunt et al. also found that 27 Gy and 26 Gy five-fraction schedules were non-inferior in terms of ipsilateral breast tumor relapse in patients with early breast cancer.[8] These findings support our hypothesis that conventional radiation therapy for partial-breast irradiation can reduce late toxicity without compromising

local tumor control.[13] The goal of adjuvant radiotherapy (RT) following primary surgery is to eradicate any possible microscopic residual disease in the operating room and/or nearby satellites.[1]

Extended periods of whole-breast radiation therapy have been linked to higher rates of mastectomy or lower use of post-lumpectomy radiation therapy.[14] Patients who receive hypofractionated whole-breast radiation therapy still require daily commuting, time off work, childcare, or other arrangements, which is why they would prefer an even shorter radiation course.[15] In Laughlin et al.'s randomized trial in 2023, UHF (25 Gy in 5 fractions) was compared to MHF (40.05 Gy in 15 fractions) as adjuvant whole-breast radiation for patients with localized breast cancer after BCS. The minimal effect of treatment was demonstrated by the fact that patient-reported quality of life (QoL) metrics changes over time were all less than one point.[12] To further reduce the burden of care, APBI was introduced as a substitute that could improve access to effective breast conservation therapy by shortening the course of treatment to a few days.[3] Burkon et al.'s findings indicate that APBI is quite acceptable in terms of toxicity and cosmetic impacts, ultimately offering patients undeniable benefits. Burkon et al.'s research supports the idea that APBI and WBI are not inferior. However, we found that APBI patients had even lower levels of toxicity.[1]

The IMPORT HIGH research utilizes a modern technology called intensity-modulated radiation treatment (IMRT), which allows for more precise dosage adjustments in the breast to better reflect the risk of relapse. A simultaneous integrated boost (SIB) is when the dose per fraction is increased to the tumor bed. By focusing on titanium clips or gold seeds inserted into the tumor bed, the boost volume is reduced. This approach allows for a conventional dose to be applied to the nearby breast tissue and a slightly lower dose to the periphery of the breast tissue where the risk of relapse is lowest. As a result, the radiation dose can be increased to the cancer bed.[5] Currently, the UK's standard of care for boost radiation therapy involves either one week of 26 Gy whole-breast irradiation followed by one week of hypofractionated sequential boost or three weeks of 48 Gy SIB.[16] However, Coles et al found no evidence that increasing the boost dose over the existing biologically equivalent standard of care dosages would be beneficial for either of the two simultaneous integrated boost (SIB) test groups.[5] While our trial included an optional sequential internal boost to a total of 48 Gy in 15 fractions or 30 Gy in 5 fractions for the MHF and UHF arms, respectively, the UK FAST-Forward only permitted a sequential boost to the tumor bed.[12] The Laughlin et al. study confirms the safety of a SIB combined with the UHF regimen. However, more time is needed to fully understand the late consequences.[12] Burkon et al. recently discovered that in elderly patients with adequate resection margins, a boost may not be necessary. This may have made certain patients' observed toxicity parameters worse, emphasizing the disparities between the arms.[1] On the other hand, SIB eases the financial burden on patients and their families by lowering travel expenses and facilitating a quicker return to work. The technique allows radiation timeslots to be used for other patients, which is an efficient use of resources for healthcare professionals.[5]

To prevent the recurrence of breast cancer in patients who have had lumpectomies for early-stage breast cancer, researchers examined whether a few days of radiotherapy to the area around the surgical cavity (APBI) could be as effective as several weeks of radiotherapy to the whole breast (whole-breast irradiation). However, based on the upper limit of the confidence interval for the hazard ratio, APBI was found to be not as effective as whole-breast irradiation in preventing breast tumor recurrence. Nonetheless, there was only a slight difference of less than 1% in the 10-year cumulative incidence of breast tumor recurrence.[3] Furthermore, there was no significant difference in the overall survival, disease-free survival, or distant disease-free interval between the two methods. Although normal tissue effects continue to accumulate beyond 5 years, the relative differences between the two methods remain stable, according to 10-year analyses of earlier Canadian and UK trials.[8] In a study by Laughlin et al., there was no significant difference in cosmesis worsening reported by providers between UHF and MHF treatments at 1, 2, and 3 years. Additionally, patients who received UHF treatment reported fewer radiation skin burns than those who received MHF treatment.[12] Several clinical

trials and meta-analyses have confirmed the importance of adjuvant radiotherapy for tumor control in the treated breast, supporting breast conservation for patients with early-stage disease.[17]

The following text has already been written and contains information about adjuvant radiation side effects. Skin erythema was the most commonly reported occurrence, with 19.9% and 66.5% in the APBI and WBI arms, respectively. There were no grade ≥ 2 toxicities observed in the APBI group in terms of late adverse effects. Skin fibrosis was the most frequently reported occurrence in both the APBI and WBI arms, with 4.5% and 11.2%, respectively.[1] Although our study did not demonstrate equivalency to whole-breast irradiation, the small differences in 10-year IBTR and recurrence-free interval without a significant difference in distant disease-free interval, disease-free survival, and overall survival may be acceptable to small breast cancer populations similar to those enrolled in other trials. Therefore, the safety of APBI may become important when choosing radiation techniques.[3] None of the UHF arms were found to be inferior to the MHF arm in terms of ipsilateral breast tumor relapse. There was a difference between 27 and 26 Gy in terms of normal tissue effects in the breast or chest wall.[12] The RAPID trial found that whole-breast irradiation caused worse grade 2 acute toxicity, while APBI caused worse grade 2-3 late toxicity. However, we did not observe a comparable pattern in our trial. Similar toxicity to whole-breast irradiation has been documented in other trials investigating various partial breast irradiation techniques.[3] The 26 Gy FAST-Forward trial's schedule is safe and effective, while also being practical and significantly less costly for both patients and healthcare services. It is also likely safe for patients who need regional radiation therapy, and this strategy is being formally evaluated in a randomized FAST-Forward substudy that compares 26 Gy in five fractions with 40 Gy in 15 fractions.[8]

CONCLUSION

Whole-breast irradiation and partial-breast irradiation are effective treatments for breast cancer, with both methods having non-inferiority in terms of local relapse and late normal-tissue effects. Adjuvant radiotherapy (RT) is used to eradicate residual disease in the operating room and nearby satellites. Patients with localized breast cancer may prefer shorter radiation courses to reduce care burden. Intensity-modulated radiation treatment (IMRT) is used to adjust doses in breast cancer patients, with SIB reducing boost volume. Adjuvant radiotherapy is crucial for tumor control in the treated breast, supporting breast conservation for early-stage disease.

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