Review

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New Approaches in Breast Cancer Radiotherapy

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ABSTRACT

Breast cancer stands as the most prevalent malignancy, necessitating a well-established approach to its management due to its sustained prevalence over decades. The implementation of intensive treatments, combining various modalities, has yielded excellent survival outcomes. Consequently, the optimization of quality of life and the mitigation of long-term side effects emerge as critical considerations for clinicians. As a result, discussions regarding treatment de-intensification strategies have been initiated for all treatment modalities, including surgery, radiotherapy (RT), and chemotherapy. RT plays a crucial role in adjuvant therapy. The efficacy of RT in disease control and overall survival across all stages of breast cancer has been demonstrated in numerous clinical trials and meta-analyses utilizing extensive datasets. However, advancements in genetic tumor profiling and improved identification of disease subgroups have prompted a reevaluation of RT omission in low-risk groups as a strategy for treatment de-intensification. Conversely, technological improvements and shortened total treatment times with hypofractionation make RT a secure and feasible option for enhancing local control and survival with minimal impact on the quality of life.

Keywords: Breast cancer; oncotype Dx; radiotherapy; review

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Key Points

- Breast cancer is globally the most prevalent cancer type and has a favorable prognosis with a multi-modality approach.
- Radiotherapy plays a crucial role in the adjuvant setting, and its benefit to local control and survival has been demonstrated by numerous randomized trials and meta-analyses with large datasets.
- Recently, most efforts in breast cancer therapy have focused on better understanding the biology and genetics of tumors and de-intensifying treatment accordingly.
- Contemporary studies aim to omit radiotherapy in low-risk patients. On the other hand, with advancements in technology and effective utilization of hypofractionation, evolved radiotherapy emerges as a more feasible option by minimizing radiation-related long-term toxicities and reducing its burden on the national healthcare system.

Introduction

Innovations in Fractionation Schemes

Adjuvant radiotherapy (RT) is not only effective in achieving local control but also contributes to the overall survival of patients at all stages of breast cancer (1, 2). Consequently, adjuvant RT is widely used in breast cancer treatment. However, conventional fractionation necessitates the delivery of a 45–50.4 Gy dose to the whole breast, spread over 25–28 fractions, taking 5–5.5 weeks. In addition to this, a boost dose is required after breast-conserving surgery, which is known to enhance local control rates, usually administered in 4 to 8 fractions, delivering a 10–16 Gy dose (3). This can extend the total treatment time to 7–8 weeks. The prolongation of total adjuvant RT time has led to shifts from breast-conserving approaches to mastectomy for some patients and the omission of RT for others (4). Furthermore, given that breast cancer is the most common cancer type globally, the total treatment time is a significant concern for national healthcare systems and the appointment loads of clinics (5).

However, concerns regarding hypofractionation were raised due to its potential long-term side effects on normal tissues, the inadequacies of previous RT techniques in normal tissue sparing, and the longer life expectancy of breast cancer patients. Nevertheless, advancements in RT technology prompted efforts to shorten the total treatment time for

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early-stage, low-risk breast cancer patients approximately two decades ago. These endeavors yielded local control outcomes that were found to be non-inferior when compared to conventional fractionation. Following initial attempts with moderate hypofractionation (a total of 15–16 fractions without a boost), new schemas evolved into ultra-hypofractionation (a total of 5 fractions), demonstrating their safe applicability in early-stage breast cancer. Some of the studies that have influenced our clinical practice are summarized in Table 1.

While the role of hypofractionation has been established in early-stage breast cancer, data on the use of hypofractionation for chest wall irradiation, regional nodal irradiation, post-neoadjuvant treatment, and patients undergoing reconstruction has not yet matured. However, there is still some data available from the START A and B trials, as well as Chinese and US studies. The START A and B trials were non-inferiority trials comparing hypofractionated whole breast irradiation (HF-WBI) and standard fractionated whole breast irradiation (SF-WBI) for early-stage breast cancer. In these trials, post-mastectomy chest wall RT was administered to 15% and 8% of the patients, respectively. These trials demonstrated that HF-WBI was non-inferior to SF-WBI in terms of disease control and acute and late toxicities. Even though the number of patients receiving post-mastectomy radiotherapy (PMRT) was relatively low compared to the total study population, increased side effects related to mastectomy were not observed in these trials.

In the Chinese study, 820 patients underwent PMRT+RNI (regional nodal irradiation) with a regimen of 43.5 Gy/16 fractions. PMRT was delivered using electron energy, and a 2D technique was employed for irradiation of the supraclavicular field. Internal mammary nodes (IMN) were not included. The study's results indicated similar outcomes for disease control and late adverse effects (such as radiation

Table 1. Randomized studies that have altered the clinical practice

Study	Duration	Patient no	Age	Follow-up (years)	Node positive (%)	RT dose	Local control (%)	Side effects
Ontario CANADA trial (6)	1993-1996	1234	24.7% <50	10	0	50 Gy/25fr vs 42.5 Gy/16fr	93.3 93.8	Similar late toxic effects for skin and breast cosmesis
Royal Marsden (7)	1986-1998	1410	54.5 (mean)	9.7	33	50 Gy/25fr vs 39 Gy/13fr vs 42.9 Gy/13fr	92.1 90.9 92.9	39 Gy arm has the best results for both cosmesis and skin changes, 42.9 Gy arm has the worst results
START-A (8)	1999-2002	2236 (Mastectomy included, 15%)	57 (mean)	9.3	29	50 Gy/25fr vs 39 Gy/13fr vs 41.6 Gy/13fr	93.3 91.9 94.4	Lower rates of late side effects with photographic evaluation and PRO for 39 Gy arm
START-B (9)	1999-2001	2215 (Mastectomy included, 8%)	58 (mean)	10	24	50 Gy/25fr vs 40 Gy/15fr	94.8 96.2	Lower rates of late side effects with photographic evaluation and PRO for 40 Gy arm
HYPO (10)	2009-2014	1854 (DCIS included, 13.3%)	59 (median)	9	9.8	50 Gy/25fr vs 40 Gy/15fr	96.7 97	Skin changes and pain was seen in low rates and similar between dose groups. Patient satisfaction for breast cosmesis was high for both groups. RT boost did not seem to increase breast induration.
FAST (11)	2004-2007	915	62.9 (mean)	9.9	0	50 Gy/25fr vs 30 Gy/5fr vs 28.5 Gy/5fr (once a week for 5weeks)	99 99 98.7	NTE was increased in 30 Gy arm compared to 50 Gy arm. 28.5 Gy has similar results with conventional arm.
FAST-FORWARD (12)	2011-2014	4096 (mastectomy included, 6.4%)	61 (median)	5.9	18.3	40 Gy/15fr vs 27 Gy/5fr vs 26 Gy/5fr (over one week)	97.9 98.3 98.6	Moderate to marked NTEs for dose groups were 9.9%, 15.4% and 11.9% respectively. Twenty-six Gy regimen has similar effects on normal tissue with 40 Gy regimen.

NTE: Normal tissue effects; PRO: Patient reported outcomes; RT: Radiotherapy

pneumonitis, lymphedema, ischemic heart disease, and shoulder), while acute toxicities were significantly better in the HF-PMRT group compared to the SF-PMRT group (3% vs. 8%). An important criticism of this study is that the techniques used in this study are no longer in use in Europe, US, or our country (13).

Another study for HF-PMRT was conducted in the US, designed as a phase II prospective trial, and included 69 patients for PMRT+RNI, with 54% of them including IMN irradiation, at a dose of 36.6 Gy in 11 fractions. High-risk patients (close margins, lymphovascular invasion +, triple-negative, young age) were eligible for the study, and breast reconstruction was performed for 45% of the patients. The 5-year local recurrence rates and grade 2 acute skin toxicity were reported as 4.6% and 24%, respectively. While there were no grade 3 late side effects, the rate of grade 3-4 complications related to reconstruction was reported as 35% with this fractionation scheme (14). The long-term rates of cardiac, pulmonary, and chest wall toxicities were all <1% in all four of these studies (15).

Additionally, numerous retrospective studies in the literature report the safe administration of hypofractionated regimens for PMRT and RNI (15). Despite the encouraging results obtained from these initial efforts, further randomized studies are required to validate the use of hypofractionated schemes for routine application in clinical practice, particularly after breast reconstruction. The results of the FABREC trial recently presented at the 2023 American Society for Radiation Oncology (ASTRO) Annual meeting (16) indicated that both accelerated and standard courses of treatment were equally effective in preventing the recurrences after immediated implant based reconstruction and had the same level of side effects. The RT-CHARM study is still ongoing. FAST Forward nodal substudy is primarily powered to demonstrate non-inferiority in terms of late normal tissue toxicity with an ultrafractionation scheme. Definitive assesment of non-inferiority will be available only at the 5-years analyses (17). Until now there is no data for offering hypofractionated comprehensive nodal RT following neoadjuvant chemotherapy for patients with locally advanced breast cancer.

The Role of Tumor Biology in Breast Radiotherapy

Omission of Radiation Therapy Using Biomarkers After Breast-Conserving Surgery

The low rates of local recurrence observed in breast cancer patients with ultra-low-risk factors raise the question of omitting radiotherapy. Several studies have sought to identify women with early breast cancer who would not derive significant benefit from RT. Long-term outcomes from two randomized trials, namely the CALGB 9343 and PRIME II trials, have indicated increased rates of local recurrence with no impact on survival when radiation was omitted after breast-conserving surgery in women aged 65 years or older (18, 19). Therefore, considering the omission of RT in elderly women with stage I, ER-positive, lymph node–negative disease who are committed to endocrine therapy remains a standard of care option. However, accelerated partial breast irradiation (APBI) or other hypofractionated schedules might serve as alternatives to the omission of RT to enhance local control rates when only endocrine treatment is prescribed. The recently published prospective cohort LUMINA trial focused on breast cancer patients aged at least 55 years who underwent breast-conserving surgery for T1N0, grade 1–2 luminal A subtype of breast cancer, along with adjuvant endocrine therapy. The Luminal A subtype was defined by estrogen receptor positivity of ≥1%, progesterone receptor positivity of >20%, negative Her-2 status, and a Ki-67 index of 13.5% or less. The incidence of local recurrence was found to be 2.3% over 5 years, but longer follow-up will be necessary for a comprehensive assessment (20).

Recent studies focus on using biomarkers such as oncotype DX recurrence score and genetics to guide adjuvant systemic therapy decisions. Numerous prospective studies are underway to evaluate the use of clinicopathologic factors and assays in better identifying low-risk patients for whom adjuvant breast RT may be safely omitted. One such study is the randomized De-Escalation of Breast Radiation trial, which, with an oncotype recurrence score of less than or equal to 18, aims to assess the expansion of RT omission to women aged 50 to 69 years (21). The EXPERT trial is randomizing patients aged 50 years or older with stage I, grade 1 or 2, tumor size 2 cm or less, and a Prosigna (PAM50) assay indicating a luminal A biological subtype into RT and RT omission arms (22).

In addition to these randomized trials, two single-arm prospective trials are ongoing. The IDEA trial targets women between 50 and 69 years with an Oncotype DX score of less than or equal to 18, while the single-arm PRECISION trial focuses on women between 50 and 75 years with T1 tumors and low risk according to the PAM50 molecular profile (23, 24). The novel Profile for the Omission of Local Adjuvant Radiation (POLAR) genomic signature, based on loco-regional recurrence (LRR) biology, may identify patients at low risk for LRR despite not receiving RT and, thus, may be candidates for RT omission (25).

Omission of Regional Nodal Irradiation in Node-Positive Breast Cancer With the Use of Biomarkes Assays

An individual patient data meta-analysis involving 14,324 women across 16 trials revealed that regional node RT significantly reduced breast cancer mortality and all-cause mortality in trials conducted after 1980. Estimated absolute reductions in 15-year breast cancer mortality were 2.7% for individuals with one to three positive axillary lymph nodes (26). Despite the proven benefit of regional irradiation for patients with low axillary involvement, it is crucial to identify subgroups of patients who may not require PMRT or regional nodal irradiation.

In cases of lymph node-positive breast cancer subtypes, such as triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer, systemic therapy is typically administered before surgery. However, for patients with node-positive estrogen receptor (ER)-positive/HER2-negative breast cancer, surgery may be the primary intervention. Several studies have indicated that the oncotype recurrence score (RS) can identify patients at the highest risk for locoregional recurrence in the node-positive setting (27, 28). For instance, the SWOG S8814 trial demonstrated that the estimated cumulative incidence of locoregional recurrence rates over 8.6 years was 9.7% for patients with low-risk RS and 16.5% for those with high-risk RS in ER+, node-positive breast cancer (29).

Taking into consideration the above data, the Canadian Cancer Trials Group recently initiated the TAILOR RT/MA.39 trial. This trial randomizes lumpectomy or mastectomy patients with one to three nodal macrometastases or micrometastases, or those classified as pT3N0, with an oncotype RS of less than or equal to 25, to receive regional nodal irradiation or not. The objective is to determine whether PMRT or regional nodal irradiation can be safely omitted in this specific group of patients (30).

Technological Advances

Over the course of several decades RT techniques have undergone significant advancements. The initial approach involved 2D planning, which did not incorporate the use of computerized tomography (CT) imaging and the delineation of critical organs. This method was subsequently replaced by three-dimensional conformal radiotherapy (3D-CRT). Following this, the forward planning technique known as Field-in-Field (FINF) was introduced, utilizing the movement of multi-leaf collimators to mitigate the presence of hot spots within the radiation therapy (RT) field. FINF has proven to be instrumental in reducing acute skin complication rates and enhancing breast cosmesis when compared to the conventional 2D RT approach (31, 32).

Subsequently, Intensity Modulated Radiation Therapy (IMRT) with inverse planning became available, clinicians the capability to optimize RT plans according to the specific conditions prior to dose calculation. IMRT has been shown to provide better preservation of breast skin and critical organs and to achieve a more homogeneous dose distribution within the target area compared to 3D-CRT (33). However, the prolongation of treatment duration and the displacement of the breast due to respiratory motion have introduced setup uncertainties. With the introduction of respiratory control systems IMRT can be safely administered for breast, chestwall and comprehensive regional irradiation. The volumetric arc therapy (VMAT) technique, which is essentially rotational IMRT, made possible by the continuous movement of the gantry, has shortened treatment times and enabled the creation of RT plans with similar quality dose distribution to IMRT (34). With the VMAT technique, it is possible to generate more reliable plans in terms of dose distribution and delivery compared to 3D-CRT. This has also been reflected in clinical results, with Grade 1 skin toxicities being reported at around 30%, and physician-reported cosmetic satisfaction rates reaching 98% (35).

Furthermore, a specific technology, helical tomotherapy (HT), can also be utilized in breast irradiation. While it is more successful in terms of hot spots and ipsilateral critical organ protection compared to other techniques, it significantly increases the low-dose area (36). HT's dosimetric advantages are particularly highlighted in bilateral breast and chest wall irradiation. However, due to the extended beam-on-time duration, uncertainties during treatment increase. Therefore, the VMAT technique, which provides results closest to HT, may be preferred for similar patients (37, 38).

Darby et al. (39), examining the results of 2,168 breast cancer patients treated between 1952 and 2001, it was reported that every 1 Gy increase in the mean dose to the heart led to a 7.4% increase in the rate of coronary disease. Although in the present day, deaths from cardiac events in breast cancer are almost non-existent, this study underscores the importance of protecting the heart during radiation therapy. Indeed, current guidelines have limited mean heart doses to <2.5 Gy for breast only RT (40).

The optimal parameter for evaluating cardiac toxicity is a subject of debate. The literature emphasizes the importance of paying attention to doses delivered to the left anterior descending coronary artery (LAD) (41). Given that LAD and the cardiac apex are anatomically located more anteriorly, they are more likely to be exposed to radiation during treatment. Even when mean heart doses are within normal limits, these areas may still receive higher doses.

Reducing heart doses can be challenging, particularly during left breast or chest wall irradiations where internal mammary lymph nodes need to be included in the radiation field. Deep Inspiration Breath Hold (DIBH), hybrid planning, and positioning the patient in the prone position offer solutions to this problem.

DIBH involves holding one's breath during the deep inspiration phase, allowing the heart to move away from the chest wall, thereby achieving the necessary distance for a dose reduction between the target and the heart. It can be applied using surface guidance or a spirometer, with patient compliance being essential (42). While it is generally emphasized in left-sided irradiations, studies have also demonstrated dosimetric advantages for heart and lung parameters in right-sided irradiations (43). In patients treated with this technique, there is a significant dose reduction in level 1–2 axilla that incidentally receive doses from tangential fields (44). Importantly, in the ACOSOG Z0011 and AMAROS studies, which focused on axillary treatment de-escalation in early-stage disease, DIBH was not used. Therefore, when DIBH is applied in this patient group, attention should be paid to the delineation of the axillary target volume intended for inclusion in the RT fields.

Hybrid planning is the term used to describe the combined use of FIF, IMRT, and VMAT techniques. This allows for the optimal utilization of the strengths of each technique while minimizing their weaknesses. Dosimetric studies have shown that hybrid techniques provide a more homogeneous dose distribution and contribute to the reduction of ipsilateral lung and heart doses (45).

Another technique that can be used to reduce doses to critical organs is prone positioning. This method is particularly advantageous for patients with pendulous and large breasts in terms of skin, lung, and heart doses (46). With this technique, average lung doses can be reduced from 3.9 Gy to as low as 0.6 Gy (47). It is known that in breast cancer, smoking increases the risk of developing secondary cancers in the lungs (48). Therefore, minimizing lung doses is of great importance. Additionally, it has been demonstrated that the axillary region can be safely irradiated in the prone position (49).

In addition to innovative technologies, the reduction of treatment volumes has also been considered to minimize treatment toxicity. As a result of studies in this direction, it has been established that APBI can be performed in early-stage low-risk breast cancer. The research initially began with interstitial brachytherapy and was later confirmed with 3D-CRT and IMRT (50-52). Today, according to the guidelines of ASTRO, ABS, and GEC-ESTRO, APBI is recommended for patients with tumors <2–3 cm, estrogen receptor (ER) positive, no lymphovascular invasion, negative surgical margins (>2 mm) and older than 50 years old (53).

In breast cancer, one of the current radiation therapy techniques is intraoperative radiation therapy (IORT), which can be administered using high-dose brachytherapy, low-energy X-rays, or electrons. However, randomized studies investigating IORT have reported a significantly higher rate of local recurrence compared to the control group, which has hindered the widespread adoption of this technique in current practice. Nevertheless, it should be noted that among these studies, TARGIT-A has faced criticism from a statistical perspective, while ELIOT has been criticized for patient selection (54, 55).

Carbon-ion and proton irradiations have a unique feature called the Bragg peak. These beams, characterized by a high linear energy transfer

(LET), do not advance further into the tissue once they reach the maximum dose. As a result, normal tissues located behind the target receive much better protection compared to photon irradiations. In fact, studies involving proton and carbon-ion irradiations have demonstrated their advantages in protecting surrounding organs such as the heart and lungs and minimizing low-dose area. However, initial studies with proton therapy raised concerns about poor cosmetic outcomes (56). While technological advancements in proton therapy have seemingly addressed this issue by increasing the number of radiation fields in treatment plans, excellent dosimetric results can already be achieved with techniques like DIBH and prone positioning. Moreover, considering the cost of proton irradiation, this technique has not yet become a routine practice. On the other hand, the outcomes of proton and photon irradiation for internal mammary chain are currently being evaluated in the ongoing RTOG 3510 trial (57).

Finally, MR-guided radiotherapy (MRgRT) has emerged as a very recent method in the treatment of breast cancer. This system allows for on-couch online adaptive planning before each fraction and the ability to monitor the target online during treatment. Furthermore, MR imaging provides superior soft tissue images. Studies have highlighted the prominence of this technology in prone-positioned APBI applications and preoperative RT applications (58, 59). The patient's time on the treatment table is extended due to routine workflow. Besides, this technology has no superiority compared with other technologies so that it is not suggested to be used in daily practice. However, it is a unique technology that can be safely applied in compliant patients.

Conclusion

Breast cancer stands as the most prevalent malignancy, necessitating a well-established approach to its management due to the sustained prevalence over decades. The implementation of intensive treatments, combining various modalities, has yielded excellent survival outcomes. Consequently, the optimization of quality of life and the mitigation of long-term side effects emerge as critical considerations for clinicians. As a result, discussions regarding treatment de-intensification strategies have been initiated for all treatment modalities, including surgery, RT, and chemotherapy.

RT plays a crucial role in adjuvant therapy. The efficacy of RT in disease control and overall survival across all stages of breast cancer has been demonstrated in numerous clinical trials and meta-analyses utilizing extensive datasets. However, advancements in genetic tumor profiling and improved identification of disease subgroups have prompted a reevaluation of RT omission in low-risk groups as a strategy for treatment de-intensification. Conversely, technological improvements and shortened total treatment times with hypofractionation make RT a secure and feasible option for enhancing local control and survival with minimal impact on the quality of life.

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