Review Article

Future directions of radiation therapy in the management of breast cancer

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Abstract: Over the past several decades, radiation therapy has played a key role in the management of breast cancer. Although the oncologic benefits of radiotherapy are well established, the landscape of breast oncology is ever changing and evolving, and radiation is no exception. Radiation oncologists are pursuing new technology and techniques to maintain their oncologic benefits, while minimizing potential side effects and treatment burden. This has led to clinical trials using therapy de-escalation of radiation in select patients with favorable characteristics. Multiple studies are using modern genetic testing, such as Oncotype Dx and PAM50, to identify low-risk women that may potentially have radiation omitted in favor of endocrine therapy alone. Another area of active investigation is the de-escalation of therapy in node-positive patients, using genetic testing or response to neoadjuvant systemic therapy as prognostic factors. The use of hypofractionation has become standard of care in the breast conservation setting, but its use in the post-mastectomy is an area of interest in multiple ongoing studies. Partial breast irradiation (PBI) is another evolving avenue to shorten treatment time, with multiple modalities available. Other investigators are attempting to alter the traditional treatment paradigm of breast cancer by administrating radiation in the preoperative setting rather than postoperative. New technologies such as proton therapy and stereotactic body radiation therapy (SBRT) have made their way into ongoing trials as well. In the setting of oligometastatic breast cancer, several trials are attempting to use SBRT as metastasis directed therapy to improve oncologic outcomes. In this review, we cover several ongoing important breast radiation clinical trials and how they will impact breast cancer care.

Keywords: Radiation therapy; breast cancer; clinical trials; adjuvant radiation; breast radiation

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Introduction

Breast cancer management requires a multidisciplinary approach with a combination of surgery, radiation therapy, and systemic therapy. The use of radiation therapy remains a pivotal part of breast cancer treatment for the majority of women affected, where it has been shown to reduce locoregional recurrences and improve survival (1-3). The goal of any therapeutic treatment is to maximize disease control while minimizing treatment related toxicities. Over time, as with surgical techniques and systemic therapies,

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the therapeutic index of radiation continues to improve. There are now newer, more advanced radiation planning techniques and patient-specific targeted approaches, allowing for fewer toxicities while maintaining the benefit of radiation. With improvements in systemic therapies and greater understanding of the wide array of breast cancers, there are now several different settings where both de-escalation and escalation of radiation therapy may play a role. Clinical trials are pivotal in exploring these variabilities in treatments. Current important ongoing trials include the de-escalation of radiation in favorable patients, the use of shorter radiation treatment regimens, the use of newer or advanced radiation techniques in attempts to minimize toxicities, pre-operative radiation techniques, and using metastasis directed radiation therapy in patients with oligometastatic disease. These trials will help optimize the use of radiation therapy in patients with breast cancer.

Methods

This manuscript describes important ongoing trials using radiation therapy for breast cancer patients. Using clinicaltrials.gov (4) as the source of available and ongoing radiation and breast cancer specific clinical trials, select trials are described below. Most of the trials discussed are large cooperative group trials or other randomized, multi-institutional or important phase I–II trials exploring the safety and efficacy of newer radiation applications or techniques. The majority of discussed trials are actively recruiting at the time of this manuscript preparation, with the exception of a few that are recently closed after meeting accrual.

De-escalation in favorable risk breast cancers

In early-stage breast cancer patients, there is a clear spectrum of disease recurrence risks based on patient and tumor specific characteristics (5-8). Newer genetic profiling techniques including Oncotype Dx and PAM50 have also shown to predict for more favorable outcomes in early-stage breast cancers (9-11). The question remains for many of these patients with favorable disease characteristics if therapy de-escalation, including the omission of radiation, is an acceptable treatment without a greater risk of recurrence. TAILORX was a phase III trial of over 10,000 women with hormone receptor (HR) positive, HER2 negative, node negative breast cancer used the Oncotype DX Breast Recurrence score, a 21-gene expression test, to assess their risk of distant disease recurrence, grouping them into a risk category based on their recurrence score. The trial results were practice changing, demonstrating that the majority of eligible patients (those with low and some intermediate Oncotype DX recurrence scores) can be safely treated with endocrine therapy (ET) alone, and avoid chemotherapy without compromising disease control and survival (12). ASCO guidelines help guide therapeutic decisions using these types of genomic biomarker tests: the Oncotype DX Recurrence Score and a similar 50 gene panel test, PAM-50 (13). Similar to de-escalation of systemic therapy, there have been past trials looking at omission of adjuvant radiation in favorable early-stage breast cancer patients (14-18). As depicted in *Table 1*, these trials have shown that even with favorable disease characteristics (namely HR positivity, small volume, node negative disease and older age), the addition of radiation to ET provides a statistically significant local disease control benefit, although the clinical significance of this is debatable. Based on these results, omission of radiation is a consideration in select patients—generally older individuals with favorable disease characteristics, who are willing to take at least 5 years of ET and willing to accept a higher risk of local recurrence.

Current ongoing clinical trials aim to take this question a step further utilizing genomic biomarker testing. The IDEA trial is a multi-center registry trial studying omission of radiation in women ages 50–69 with pT1N0 breast cancers, HR positive, HER2 negative with an Oncotype DX recurrence score of ≤18, who will receive a minimum of 5 years of ET (19). This trial recently completed accrual and data are maturing. Similarly, the PRECISION Trial is enrolling patients ages 50–75 with pT1N0 breast cancer, HR positive, HER2 negative, grade 1–2, that are deemed low risk by the genomic marker test, PAM50 (20). In Ontario, the LUMINA trial is enrolling patients age 55+ with pT1N0, grade 1–2 breast cancers, Luminal A (with low Ki-67 of <14%) onto their registry trial treating with ET alone (21). Finally, the EXPERT trial is a randomized, phase III non-inferiority trial assessing women with favorable risk breast cancer based on PAM50, randomized to ET alone *vs.* adjuvant radiation with ET, with a primary endpoint of 10-year local recurrence (22). All of these studies, summarized in *Table 2*, A, are aiming to use additional genomic tumor markers to better select for patients who may have low recurrence rates with ET alone, potentially allowing for omission of radiation without compromising disease control. Of note, one must take care in appropriate patient selection and counseling when

Table 1 Trials of omission of radiation in early-stage breast cancers

Trial	Patients	Trial arms	Results*	Comments
NSABP-B21 (14)	Tumors ≤1 cm, N0, invasive breast cancers, s/p lumpectomy and axillary dissection, negative margins	RT + Tam RT + placebo Tam alone	14-year IBTR: 10.2% RT + Tam; 10.8% RT alone; 19.5% Tam alone	No difference in OS
CALGB 9343 (15)	Age ≥70, pT1N0, HR+, s/p lumpectomy +/– axillary surgery, negative margins	Tam + RT Tam alone	10-year LRR: 2% Tam + RT; 10% Tam alone	No difference in 10-year OS, DM or BCSS
PRIME II (16)	Age ≥65, pT1-2N0, HR+, s/p lumpectomy and axillary staging, negative margins	ET alone ET + RT	5-year IBTR: 1.3% Tam + RT; 4.1% Tam alone	No difference in 5-year OS, DM
Princess Margaret Hospital (17)	Age ≥50, pT1-2N0, negative margins	Tam alone Tam + RT	5-year LR: 7.7% Tam alone; 0.6% Tam + RT 5-year DFS: 84% Tam alone; 91% Tam + RT	No difference in 5-year OS or DM
JNCI Pooled Analysis (18)	Stage I, ER+ and/or PR+, HER2–, oncotype score ≤18	HT alone HT + RT	5-year RFI: 93.5% HT alone; 97.9% HT + RT	No difference in distant RFI, OS, or BCSS

*, these results are statistically significant. RT, radiation; Tam, tamoxifen; HT, hormone therapy; IBTR, ipsilateral breast tumor recurrence; LRR, locoregional recurrence; LR, local recurrence; RFI, recurrence free interval; OS, overall survival; DM, distant metastases; BCSS, breast cancer specific survival.

choosing patients for omission of radiation on or off study, as medication compliance can be an issue. There have been multiple studies demonstrating poor compliance taking daily ET for 5 years in patients who omitted adjuvant breast radiation off trial, with compliance rates of only 40–60% (26,27). Furthermore, shorter courses of radiation now provide more convenient radiation options than in the past. Partly due to compliance issues, there are discussions of a phase III study of adjuvant radiation *vs.* adjuvant ET in favorable risk breast cancer patients.

De-escalation of therapy in node positive patients

Multiple clinical trials have demonstrated a benefit to treating patients with node positive breast cancer with adjuvant radiation, providing superior locoregional control (LRC) and disease-free survival (DFS) (28-31), and in the post-mastectomy setting, a cancer specific survival benefit as well (2). Even in patients with only one to three positive nodes involved, this benefit held true based on a large meta-analysis of over 8,000 post-mastectomy patients, with significant absolute improvements in locoregional recurrence rates (LRR) (by 16.5%), any recurrence (by 11.5%) and a 7.9% reduction in breast cancer specific mortality (71% *vs.* 80%) (2). A caveat of this meta-analysis is many women had received older, less effective chemotherapy, and outdated radiation techniques so in the modern era, this benefit to radiation may be different. Additional studies are underway to help answer this question of whether de-escalation of radiation is possible in patients with low nodal disease and favorable risk factors.

The UK recently completed and reported early results from the SUPREMO trial assessing whether adjuvant radiation can be safely omitted in patients with one to three involved nodes. This trial recruited women with pT1–2N1, pT3N0, or pT2N0 tumors and lymphovascular invasion or grade 3 disease who had undergone mastectomy, and if node positive, axillary dissection. Women were then randomized to post-mastectomy radiation (PMRT) or no radiation, with the primary endpoint being 10-year overall survival (OS). While their data needs to mature to assess disease specific outcomes, they reported on pre-specified quality of life endpoints at 2 years, demonstrating slightly worse patient reported chest wall symptoms in the PMRT arm compared to no radiation, although the difference was small and unlikely to be of clinical significance. Interestingly, the use of chemotherapy (and not PMRT) was associated with worse arm and shoulder symptoms, suggesting the multifactorial role all therapies have in treatment related

Table 2 Radiation de-escalation trials

Trial name	Enrollment criteria	Study arms	Study type	Primary outcomes
A: Omission of radiation trials*				
IDEA (19)	Age 50–69, pT1N0, HR+, HER2–, Oncotype Dx Score ≤18	ET alone	Registry trial	5-year LRR
PRECISION (20)	Age 50–70, pT1N0, HR+, HER2–, grade 1–2, low-risk luminal A by PAM50	ET alone	Registry trial	5-year LRR
LUMINA (21)	Age 55+, pT1N0, G1–2, luminal A	ET alone	Registry trial	5-year IBTR
EXPERT (22)	Age 50+, pT1N0, HR+, HER2–, luminal A subtype by PAM50	RT + ET; ET alone	Randomized, phase III, non-inferiority	10-year LR
B: De-escalation in node-positive patients				
TAILOR RT (23)	Age 40+, low risk oncotype (≤18), 1–3 positive nodes, s/p BCS or mastectomy	WBI following BCS or No RT following mastectomy	Randomized, phase III	10-year BCRFI
		WBI + RNI following BCS or CW + RNI following mastectomy		
NSABP B-51 (24)	cT1–3N1 (biopsy proven N1), s/p NAC with nodal pCR	WBI following BCS or No RT following mastectomy	Randomized, phase III	10-year IBC-RFI
		WBI + RNI following BCS or CW + RNI following mastectomy		
A011202 (25)	cT1–3N1, s/p NAC with positive sentinel node	ALND + RNI (excluding dissected axilla)	Randomized, phase III	5-year IBC-RFI
		RNI (including axilla)		

*, all of these trials assume patients will receive endocrine therapy for at least 5 years. ET, endocrine therapy; RT, radiation therapy; WBI, whole breast irradiation; RNI, regional node irradiation; CW, chest wall; BCS, breast conservation surgery; LRR, locoregional recurrence; IBTR, ipsilateral breast tumor recurrence; LR, local recurrence; BCRFI, breast cancer recurrence-free interval; IBC-RFI, invasive breast cancer recurrence free interval.

toxicities (32). A similar, ongoing phase III non-inferiority trial from the Canadian Cancer Trials Group, MA39, is using the Oncotype Dx recurrence score as part of their enrollment criteria. Patients over 40 with low-risk scores (<18) with 1–3 positive nodes following lumpectomy or mastectomy are randomized to regional nodal radiation *vs.* omission of regional nodal radiation, with a primary endpoint of breast cancer recurrence free interval (23). These trials will help establish the role of adjuvant nodal radiation in more specific settings of patients with one to three positive nodes.

Another important predictor of LRR is disease response to neoadjuvant chemotherapy, with the biggest predictor of LRR being pathologic response to neoadjuvant chemotherapy, particularly response in the nodes (33). This led the way to the ongoing randomized phase III cooperative group trial, NSABP B-51, enrolling patients with cT1–3, biopsy proven N1 breast cancer who have had a complete pathologic response in the nodes following neoadjuvant chemotherapy. Patients who undergo lumpectomy are randomized to whole breast irradiation +/– regional nodal irradiation. Patients who undergo mastectomy are randomized to no radiation or chest wall and regional nodal irradiation. The goal of the trial is to evaluate if the addition of radiation will significantly reduce the rates of breast cancer recurrence-free interval in these favorable patients, with secondary endpoints including cosmetic outcomes, quality of life differences and molecular predictors of recurrence (24).

De-escalation of nodal treatment aims to minimize an important late toxicity of lymphedema. Both the extent of axillary surgery and the use of nodal radiation contribute to this risk. Thus, another avenue under exploration is de-escalation surgically. ACOSOG Z0011 demonstrated in

breast cancer patients who are clinically node negative with 1–2 positive sentinel nodes, omitting further axillary dissection is non-inferior to sentinel lymph node biopsy (SLNB) alone, in terms of 10-year OS and DFS (34). AMAROS was a similar trial randomizing clinically node negative patients with a positive SLNB to either completion axillary dissection *vs.* axillary nodal radiation, with no difference in axillary recurrence, DFS or OS, but did show a significantly higher rate of lymphedema in the axillary dissection arm (23% *vs.* 11%) (35). The recently presented 10-year update again demonstrated no difference in OS (36). While these trials demonstrate axillary radiation is appropriate for most clinically node negative, sentinel node positive patients, this question has not yet been assessed in a randomized trial for patients who receive neoadjuvant chemotherapy. There is some non-randomized evidence suggesting it is acceptable to omit axillary dissection in patients with a positive sentinel node who receive adjuvant regional nodal radiation (37). There is an ongoing randomized trial from the Alliance cooperative group trial, A011202 enrolling patients with cT1–3, N1 breast cancer who have a positive sentinel node following neoadjuvant chemotherapy, randomizing them to either completion axillary dissection *vs.* adjuvant axillary radiation. It will evaluate whether radiation is non-inferior to axillary dissection in terms of breast cancer recurrence free interval (25). For now, the standard is completion axillary dissection for positive sentinel node biopsy following neoadjuvant chemotherapy, with an NCCN category 2b for no further dissection if getting nodal radiation (38). *Table 2*, B demonstrates the ongoing clinical trials studying de-escalation in the node positive setting.

Hypofractionated radiation in post-mastectomy patients

One challenge of adjuvant radiation for breast cancer patients is a logistical one. Typically, radiation is given on weekdays for 4–6 weeks, which can be difficult for patients and caregivers. In recent decades for breast only treatments, radiation hypofractionation (using higher than 2 Gy per fraction treatments given over a shorter number of days) has improved this challenge, allowing for a more convenient, cost-effective treatment course. Multiple trials have established moderately hypofractionated radiation given over 3–4 weeks as the standard for early stage, post-lumpectomy breast cancer patients rather than the historically used standard fractionated radiation course over 6 weeks, with equivalent disease control endpoints, and no increase in acute or late radiation related side effects (39-41). These studies even demonstrated improved acute toxicities, less fatigue, and improved late cosmesis with hypofractionation (39-41). Hypofractionation for post-lumpectomy radiation has even been taken a step further, now with five fraction radiation regimens treating the whole breast (the FAST or FAST-FORWARD regimens), showing equivalent outcomes compared to 4–6-week courses, although this regimen has been slow to adopt in many countries perhaps due to awaiting recently reported 10-year outcomes (42,43). A 3–4-week course of hypofractionated radiation is considered standard for the majority of women requiring whole breast irradiation alone following lumpectomy for invasive or *in situ* breast cancer (44). Less clear is the role of hypofractionated radiation in the post-mastectomy and node positive setting. Most of the hypofractionation trials were done in women undergoing lumpectomy. There was a recently reported phase III single institution trial from China of 820 women who underwent mastectomy without reconstruction with at least pT3–4 and pN2a breast cancers, randomized to a 5-week standard fractionated radiation course *vs.* a 3-week hypofractionated radiation course treating the chest wall and regional nodes. The results were favorable with no significant difference in 5-year LRR or late toxicities, as well as fewer acute toxicities in the hypofractionated course (45). It is important to note that this protocol used 6–9 MeV electron beams for chest wall irradiation, rather than more commonly used photons. This has led to concern of the trial's applicability to all post-mastectomy patients, particularly to women who undergo mastectomy with reconstruction. Although, there are many parts of the world including the UK where hypofractionated radiation is commonly used in the PMRT setting. In the previously mentioned SUPREMO PMRT trial out of the UK, approximately 20% of patients had reconstruction, and the majority of patients in the PMRT arm received hypofractionated radiation—although they do not comment on outcomes of this cohort of reconstructed patients.

There are ongoing trials exploring this question of hypofractionated radiation in post-mastectomy patients with reconstruction (*Table 3*). The cooperative group Alliance A221505 trial, also known as RT-CHARM is a multi-institutional, phase III, non-inferiority trial enrolling women with stage IIA–IIIA breast cancer who have undergone mastectomy specifically with reconstruction and require PMRT to the chest wall and regional nodes.

Table 3 Hypofractionation in post-mastectomy patients

Trial name	Enrollment criteria	Study arms	Study type	Primary outcomes
RT-CHARM - A221505 (46)	pT0–3, N1–2a, ypT0–3N0–2 (stage IIa–IIIa) with immediate or planned reconstruction after mastectomy	Standard PMRT over 5–6 weeks Hypofractionated PMRT over 3–4 weeks	Randomized, phase III	2-year rate of breast reconstruction complications
FABREC (47)	Clinical or pathologic Stage I–III s/p mastectomy with immediate reconstruction at time of surgery	Standard PMRT over 5–6 weeks Hypofractionated PMRT over 3–4 weeks	Randomized, phase III	6-month patient reported outcomes

PMRT, post-mastectomy radiation therapy.

Table 4 Partial breast irradiation

Trial name	PBI modality	Enrollment criteria	Study arms	Study type	Primary outcomes
CONFIRM (58)	MRI guidance	Invasive breast cancer patients eligible for PBI	PBI using real-time MRI guidance	Phase I/II	1-year patient reported outcomes, 1-year tumor control
NCT01766297 (59)	Protons	Age 50+, stage 0–II, tumor size <3.0 cm, ER+, s/p lumpectomy	40 CGE in 10 fractions PBI	Phase II	3-year FFF
NCT03940248 (60)	Protons	Age 50+, pTis–T2, N0, tumor size <3.0 cm, ER+, s/p lumpectomy	40 CGE in 10 fractions PBI	Phase II	2-year cosmetic outcomes

PBI, partial breast irradiation; FFF, freedom from failure (ipsilateral breast cancer recurrence); MRI, magnetic resonance; ER, estrogen receptor; CGE, cobalt gray equivalent.

Various types of reconstruction are allowed. These women are randomized after surgery to standard fractionated PMRT over 5–6 weeks *vs.* hypofractionated PMRT over 3–4 weeks, with the primary endpoint being non-inferior rates of reconstruction complications (re-operation, Baker 3–4 contracture) with hypofractionation at 24 months post-treatment. Additional endpoints include both disease recurrence rates and toxicities (46). A smaller institutional trial from Dana Farber Cancer Institute, the FABREC trial is also exploring this question of standard *vs.* hypofractionated PMRT following breast reconstruction, with a primary endpoint of patient reported outcomes at 6 months and secondary oncologic and clinical outcomes including photograph assessment of cosmesis (47). If these trials demonstrate non-inferiority of hypofractionated radiation in reconstructed post-mastectomy patients, it could change the standard radiation course to a more convenient, cost-effective course in the post-mastectomy setting in years to come.

Partial breast irradiation (PBI)

An alternative to adjuvant whole breast radiation for favorable risk patients is PBI, oftentimes done over a shorter time period than the standard 3–4-week course of hypofractionated radiation including Intraoperative Radiation (IORT) done as a single treatment at the time of lumpectomy (48,49). Many PBI options have been shown to be an effective adjuvant radiation treatment for patients with favorable breast cancers, with similar rates of ipsilateral breast tumor recurrence and similar acute and late toxicities, with some exceptions (50-57). Additional ongoing trials are attempting PBI using newer technologies in attempts to shrink radiation volumes even tighter or minimize low radiation dose to surrounding normal structures, with the goal of minimizing toxicity (*Table 4*). One multi-institutional phase II study is using real-time MRI guidance during radiation treatments, which allows for better visualization of lumpectomy bed targets during treatment and smaller volumes getting treated (58). Proton radiation

has dosimetric advantages to photons and in the case of PBI, may limit dose to normal ipsilateral breast tissue and other organs at risk, minimizing risk of late toxicities. There are multiple ongoing phase II trials assessing PBI using protons (59,60).

New applications of radiation technology

One newer area under exploration for breast cancer radiation is the use of stereotactic body radiation therapy (SBRT). Compared to standard radiation, SBRT delivers a more precise, higher dose of radiation per treatment, for fewer treatments—typically 5 treatments or less. Stereotactic radiation has historically been used to treat cancers in the brain or lung, but more recently, its use has been rapidly expanding to other disease sites. In breast cancer patients, SBRT is being explored as a potential PBI option both in the post-operative setting and as definitive treatment in inoperable patients. However, there are unique challenges when using SBRT to treat targets in the breast, as it requires strict immobilization for target localization, and usually requires relatively small target volumes—both of which can be issues in breast radiation. In an attempt to address some of these issues, there is a multi-institutional phase II trial using a new radiotherapy system called the GammaPod™, a radiation unit made specifically to immobilize and treat targets in the breast. The unit uses a cup where the patient's breast sits, with a stereotactic frame to immobilize the breast, and employs multiple rotating Cobalt-60 beams to converge on a small focal target. This trial is enrolling women with early-stage breast cancers up to 3 cm in size, who have undergone breast conservation surgery (61). All women are treated with SBRT on the GammaPod™, to a dose of 30–40 Gy in a total of 5 fractions, with at least 40 hours between fractions. The primary outcome of the study is quality of life, with a secondary outcome of cosmesis, with a study aim of improving quality of life and cosmesis relative to historical controls, while maintaining similar oncologic outcomes. There is a similar ongoing trial coined RAD 1802, studying the safety of a 30 Gy in 5 fraction SBRT regimen to the lumpectomy bed in favorable risk patients eligible for PBI, but using a conventional linear accelerator (62). This is a pilot study, so primary and secondary outcomes are toxicity related, as well as cosmesis.

While the above studies are in the adjuvant setting, there is also interest using the ablative nature of SBRT in inoperable patients. A recently opened pilot study is investigating the use of SBRT in women with breast cancer who are inoperable (63). Eligible participants will have cT1–4 invasive ductal carcinoma of the breast, deemed either unresectable or the patient is a poor surgical candidate, and who have a life expectancy of >6 months. All patients will undergo SBRT in 5 fractions to a total dose of 40 Gy using a conventional linear accelerator. Their co-primary outcomes are rate of grade 3 adverse events and partial/complete response rates. If successful, results may produce a viable option for definitive treatment of non-operative patients.

Another relatively newer area of technology in radiation is the use of proton therapy. Protons have certain dosimetric distribution advantages compared to commonly used photon radiation. Specifically, protons are able to deliver radiation dose to a target, while sparing dose to structures adjacent, namely posterior to the target. This is of particular interest in breast cancer, where the posteriorly located heart and lungs can be difficult to limit radiation exposure with traditional photon irradiation, particularly when requiring nodal irradiation. Previous studies have shown excess radiation dose to the heart carries risk of significant late cardiac toxicity (64,65). For this reason, protons are currently being investigated as a potential therapeutic option in breast cancer radiation. A multi-center, randomized phase III RADCOMP Consortium Trial is currently comparing traditional photon irradiation to proton irradiation in the adjuvant setting of breast cancer (66). Eligible women can have stage I–III breast cancer of either breast, after lumpectomy or mastectomy and must be proceeding with breast/chest wall radiation and comprehensive nodal radiation therapy. Their primary outcome is to compare major cardiovascular events between the two arms. The results of this trial will help define the role of proton therapy in breast cancer.

The use of intraoperative radiation therapy (IORT) is an established technology in breast cancer as an option for PBI at time of lumpectomy in select patients (56,67). There are current studies investigating new avenues using this technology. The ongoing TARGIT-B trial is a multi-center, randomized phase III trial enrolling women at high risk of local recurrence warranting whole breast irradiation (i.e., different than their initial study, TARGIT-A that used IORT as the sole PBI treatment for favorable breast cancers). Patients in both arms will receive adjuvant whole breast radiation but will be randomized to IORT tumor bed boost *vs.* a postoperative external beam tumor bed boost (68). The primary outcome is local tumor bed control,

Table 5 New applications of radiation technology

Trial name	Radiation technology	Enrollment criteria	Study arms	Study type	Primary outcomes
NCT03581136 (61)	SBRT via GammaPod™	pTis–T2N0, tumor size <3.0 cm, s/p lumpectomy	SBRT 30 Gy in 5 fractions PBI, every other day	Phase II	5-year HRQOL
RAD 1802 (62)	SBRT via linear accelerator	Age 50+, N0, tumor size <2.0 cm, ER+, s/p lumpectomy	SBRT 30 Gy in 5 fractions PBI, every other day	Registry trial	2-year rates of toxicity
SBRT BREAST (63)	SBRT via linear accelerator	Inoperable cT1–4 breast cancer	40 Gy in 5 fractions, every other day	Registry trial	5-year rates of toxicity
RADCOMP (66)	Protons	Pathologic stage I–III or post-NAC stage 0–III, s/p mastectomy, requiring PMRT	PMRT over 5–7 weeks using photons PMRT over 5-7 weeks using protons	Randomized, phase III	10-year reduction in MCE
TARGIT-B (68)	IORT	Age <46 or age >46 and one of: + LVSI, + nodes, multifocal tumor or age >46 and two of: ER–, grade 3, + margins	WBRT + EBRT tumor bed boost WBRT + IORT tumor bed boost	Randomized, phase III	5-year local tumor control

PBI, partial breast irradiation; SBRT, stereotactic body radiation therapy; HRQOL, healthcare related quality of life; PMRT, post-mastectomy radiation therapy; MCE, major cardiovascular events; IORT, intraoperative radiation therapy; WBRT, whole breast radiation therapy; EBRT, external beam radiation therapy; LVSI, lymphovascular invasion; ER, estrogen receptor; NAC, neoadjuvant chemotherapy.

with the hypothesis that the IORT boost will be superior compared to traditional external beam boost. *Table 5* describes ongoing trials using newer radiation technologies for breast cancer.

Pre-operative radiation

Traditionally, radiation has been delivered following surgery and chemotherapy, when indicated. Recently, there has been growing interest in administering radiation in the preoperative setting, with theoretic advantages of potential downstaging of tumors, more accurate tumor targeting with smaller treatment volumes, and potentially higher rates of pathologic response to neoadjuvant therapy. One hesitation to adopting this treatment paradigm is concern over further delay to surgery, particularly with traditional standard fractionated radiation over 5–6 weeks followed by recovery time, before going to surgical resection. However, now bolstered by the success seen in neoadjuvant chemotherapy and development of more accelerated radiation schedules including SBRT as previously described, interest has been renewed.

Pre-operative radiation is being investigated at Mayo Clinic, where they have a multi-institutional, single arm phase II trial enrolling women with cT1–2N0 breast cancer (69). Women undergo hypofractionated radiation for a total of 5 fractions to the whole breast, then undergo standard of care surgery 4–16 weeks after radiation. Their primary outcome is rate of pathologic complete response upon resection. Similarly, an ongoing Stanford trial, the NORDIS trial, is a randomized phase II trial examining the role of preoperative accelerated PBI enrolling patients with ductal carcinoma *in situ* (DCIS) planning to undergo breast conservation surgery, randomizing them to either upfront surgery and adjuvant radiation or neoadjuvant PBI, 30 Gy in five fractions to partial breast, followed by a 12-week delay until surgery (70). The primary outcome and goal of the study is showing the rate of complete pathologic response; they also wish to show if different DCIS subtypes exhibit different sensitivities to preoperative RT.

Other trials are attempting to shorten the preoperative radiation course even further. Using the GammaPod™ treatment machine described earlier, University of Maryland has an ongoing phase I dose-escalation trial enrolling women with cT1–2N0 breast cancers, delivering preoperative single-fraction SBRT (dose of 21–30 Gy) to the tumor, followed by breast conservation surgery (71). The primary outcomes are related to dose limiting toxicity.

While early in development and exploration of pre-operative radiation, these trials (*Table 6*) and future ones may pave the way for larger studies and a potential role of pre-operative radiation or definitive radiation in non-

Table 6 Pre-operative radiation

Trial name	Enrollment criteria	Study arms	Study type	Primary outcomes
NCT03624478 (69)	Biopsy confirmed cT0 NAC, neoadjuvant chemotherapy 2N0 with planned breast surgery	Preoperative hypofractionated RT over 5 days, followed by breast surgery	Phase II	pCR rate at time of surgery
NORDIS (70)	Biopsy confirmed DCIS <3 cm in size with planned breast surgery	Upfront surgery	Randomized, phase II	pCR rate at time of surgery
		Preoperative PBI 30 Gy in 5 fractions, followed by breast surgery		
NCT04234386 (71)	Age >45, biopsy confirmed, unifocal, T1–2N0, tumor size <3 cm, ER+/HER2–, with planned breast surgery	Preoperative single fraction RT via GammaPod™, dose escalating from 21 to 30 Gy	Registry trial	Dose-limiting toxicities

pCR, pathologic complete response; NAC, neoadjuvant chemotherapy; RT, radiation therapy; DCIS, ductal carcinoma in situ; ER, estrogen receptor.

operable patients.

Radiation therapy in oligometastatic disease setting

The idea of an oligometastatic state has been around for some time, with the potential for cure or at least long-term DFS following aggressive treatment of all known sites. There are multiple recent trials showing that metastasis directed therapy with surgery or SBRT can provide DFS and OS benefits with low toxicity rates across various cancer types (72-76). The use of SBRT for oligometastases has increased over time (72). The SABR-COMET trial is a Canadian phase II randomized trial of metastasis directed SBRT that recently reported promising long-term results. This trial enrolled patients with a controlled/treated primary malignancy and 1–5 metastases amenable to SBRT and randomized patients to standard of care palliative systemic therapy with or without SBRT to all metastases. Breast cancer patients made up one of the most common malignancies on the study. At 5 years, they demonstrated a remarkable OS benefit in the SBRT arm, with 5-year OS of 17.7% in control arm *vs.* 42% in SBRT arm. PFS was also improved as expected. Importantly, there were no differences in toxicities or quality of life between the groups (77). There are now many ongoing studies across individual disease sites assessing the role of SBRT in the oligometastatic setting. NRG-BR002 is a phase IIR/III trial of standard of care therapy with or without SBRT and/or surgical ablation for newly oligometastatic breast cancer. Patients with breast cancer involving up to four metastatic sites amenable to SBRT or surgery are eligible. This trial also is open to "*de novo*" or newly diagnosed metastatic breast cancer patients, so long as the breast primary is controlled prior to registration with surgery +/– radiation. The primary endpoint of this study is 3-year PFS and up to 8-year OS (78). A similar phase III study is being run in France, randomizing patients with "*de novo*" metastatic breast cancer to standard systemic therapy with or without SBRT, with a primary endpoint of PFS and secondary endpoints of local control and OS (79). *Table* 7 further describes these studies.

Conclusions

It is an exciting time for breast cancer research as newer surgical techniques, radiation techniques and systemic therapies are allowing patients to live longer with lower toxicities than in the past. Clinical trials are key in developing these advances in therapies. There are multiple ongoing breast cancer radiation trials that are attempting to take these advances further. The ultimate goal of any cancer directed therapy is cure with no toxicities. The trials outlined here are all attempting this very goal. For well selected, favorable patients, trials are aiming to de-escalate radiation therapy, and hopefully minimize treatment related toxicities. Other radiation trials are evaluating newer technologies with the goal of delivering safer radiation treatments. And finally, there are promising ongoing trials using escalation of radiation for metastasis directed therapy

Table 7 Oligometastatic breast cancer

Trial name	Enrollment criteria	Study arms	Study type	Primary outcomes
NRG-BR002 (78)	Metastatic breast cancer, with 4 or less metastases seen on imaging amenable to SBRT	Standard of care systemic therapy Standard of care systemic therapy + SBRT to all sites of metastases	Randomized, phase IIR/III	3-year PFS; 3-year OS
STEREO-SEIN (79)	Metastatic ER+ breast cancer with 5 or less metastases seen on imaging amenable to SBRT	Standard of care systemic therapy Standard of care systemic therapy + SBRT to all sites of metastases	Randomized, phase II	3-year PFS

SBRT, stereotactic body radiation therapy; PFS, progression free survival; OS, overall survival.

in the oligometastatic setting, which as breast cancer patients live longer, this may be a very significant role for radiation in the future. It is important for practitioners to educate themselves on these improvements and to enroll patients in ongoing trials whenever possible to help in advancing breast cancer care.

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