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Novel radiation therapy approaches for breast cancer treatment

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ABSTRACT

The role of radiation therapy in the management of breast cancer continues to evolve. For patients with early stage breast cancer, hypofractionated whole breast irradiation following breast conserving surgery now represents the standard of care based on randomized data with long-term efficacy and toxicity outcomes. Partial breast irradiation has been found, in several randomized trials, to be effective and appropriate in selected patients with the potential to reduce toxicities as compared to whole breast irradiation. The study of tumor biology and genetics and its role in radiation therapy decision making continues to grow and the advances may help identify patients where radiation therapy can be safely omitted, with future studies looking at de-intensification approaches. Recent randomized data has demonstrated a growing role for regional nodal irradiation in patients with more advanced disease, with future studies looking to identify whether nodal radiation is indicated following neoadjuvant chemotherapy or with certain favorable tumor biologies. While postmastectomy radiation therapy represents a standard approach for patients with locally advanced breast cancer, new data supports the role of hypofractionated regimens as well as its use in patients previously considered lower risk with unfavorable tumor biology. Oligometastatic disease represents a new area of study in breast cancer with prospective trials underway and current data supporting consideration of techniques such as stereotactic body radiation therapy in appropriately selected patients.

Introduction

Adjuvant radiation therapy has been shown to not only reduce locoregional recurrences, but also improve survival for early stage to locally advanced breast cancer, and has been part of the standard treatment paradigm for decades [1,2]. However, over the past few years, the use of radiation therapy for breast cancer has evolved across all stages of the disease. For early stage breast cancer, the previous standard 6–7 weeks of whole breast radiation therapy (WBI) has given way to hypofractionated WBI (HWBI) as well as partial breast irradiation (PBI), shortening the course of therapy to 1-3 weeks and potentially reducing treatment toxicities [3-5]. Further consideration of de-escalation of treatment is underway with consideration of intraoperative radiation therapy (IORT) and the use of endocrine therapy alone [5-7]. In locally advanced breast cancers, the role of regional nodal irradiation (RNI) continues to grow and new techniques to deliver postmastectomy radiation therapy are available. Finally, in patients with metastatic disease, a new paradigm of oligometastatic disease has emerged, offering patients the opportunity to consider definitive treatment to their breast/chest wall and regional nodes as well as a limited number of metastatic sites. The purpose of this review is to present novel radiation therapy approaches in the management of breast cancer.

Whole breast irradiation

The seminal randomized trials that evaluated breast conservation therapy (BCT) as compared to mastectomy all utilized standard fractionation WBI [8-10]. These studies delivered treatment to the whole breast using standard fractionation (1.8–2.0 Gy/fraction) requiring 5 weeks of treatment. Additionally, randomized trials have demonstrated a benefit, with respect to local control, for a tumor bed boost following WBI, lengthening the course of radiation therapy to 6–7.5 weeks [11,12]. The long duration of WBI is considered 1 factor why a large number of patients are unable to undergo BCT or omit adjuvant radiation therapy [13,14].

Over the past 2 decades, HWBI has emerged as an alternative to standard WBI, reducing the course of WBI from 5 to 3 weeks (Table 1) [15-18]. The Ontario Oncology Group trial randomized

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Table 1
Randomized trials evaluating hypofractionated whole breast irradiation.

	Royal Marsden	START A	START B	Ontario oncology group	MDACC
Number of patients	1,410	2,236	2,215	1,234	287
Follow-up (years)	9.7	9.3	9.9	10.0	
Age	Mean 54.5	Mean: 57	Mean: 58		Median: 60
Dose/fraction	39/1342.9/13	41.6/13 (5 weeks) 39/13 (5 weeks)	40/15	42.5/16	42.5/16
Estrogen receptor negative	–	–	–	26%	12%
Node positive	33%	29%	24%	0%	13%
Endocrine therapy	76%	80%	88%	41%	–
Chemotherapy	14%	36%	21%	11%	31%
Local recurrence	9.6%/14.8%	6.3%/ 8.8%	4.3%	6.2%	–

Abbreviations: START = standardisation of breast radiotherapy; MDACC = MD Anderson Cancer Center.

1,234 women with node-negative breast cancer less than 5 cm and a separation of 25 cm or less (width across chest at posterior border of radiation fields) to standard or HWBI. At 10 years, no differences in the rates of local recurrence were noted (6.2% HWBI *v* 6.7% standard WBI) with similar cosmetic outcomes [15]. Similarly, the START (standardisation of breast radiotherapy) trials A and B evaluated HWBI. START A randomized 2,236 women (pT1-3a, pN0-1, M0) to standard WBI as compared to HWBI arms (39.6 or 41 Gy in 13 fractions over 5 weeks). At 10 years, no difference in locoregional recurrence was noted (8.8% 39 Gy, 6.3% 41.6 Gy, 7.4% 50 Gy) between the hypofractionated arms and the standard WBI arm with less moderate/marked induration, telangiectasias, and breast edema in the 39 Gy arm as compared to the 50 Gy arm, and no difference between the 41.6 Gy and 50 Gy arms [16]. START B randomized 2,215 women (pT1-3a, pN0-1, M0) to standard WBI or HWBI (40 Gy in 15 fractions over 3 weeks). At 10 years no difference in locoregional recurrence was noted (4.3% HWBI *v* 5.5% standard WBI) with reduced breast shrinkage, telangiectasias, and breast edema with HWBI [16]. Taken together, the results of these trials have led to the publication of evidence based guidelines which recommend the use of HWBI for most patients with early breast cancer following breast conserving surgery [3].

More recently, shorter courses of HWBI have been evaluated. The FAST trial enrolled patients (pT1-2N0) to standard WBI as compared to HWBI (28.5 or 30 Gy delivered in 5 fractions once weekly). Initial results from the 1,915 women enrolled demonstrated that 28.5 Gy had similar cosmetic outcomes to standard WBI [19]. Updated 10 year outcomes demonstrated increased normal tissue effects (shrinkage, induration, telangiectasias, edema) with the 30 Gy arm as compared to standard WBI, though rates of marked normal tissue effects were low (9.4% at 10 years). The 28.5 Gy arm had a 5.5% increased rate of moderate/marked effects as compared to standard WBI with low rates of locoregional recurrence noted in all arms [20]. Subsequently, the FAST-Forward trial which included approximately 4,000 patients evaluated 5 fraction WBI delivered in 1 week; initial outcomes of 350 patients demonstrated acute grade 3 Radiation Therapy Oncology Group (RTOG) toxicity rates of 13.6% with HWBI, 9.8% (27 Gy/5 fractions), and 5.8% (26 Gy/5 fractions) and rates of 0%, 2.4% and 0% for Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or greater toxicity with mature outcomes expected in the years to come [21].

Partial breast irradiation

The concept of PBI is derived from studies that demonstrated that the benefit of adjuvant radiation therapy following breast-conserving surgery was predominantly the prevention of recurrences in proximity to the original tumor and that residual disease was within close proximity to the lumpectomy bed [22,23]. Multiple techniques are available to deliver PBI including interstitial brachytherapy, applicator brachytherapy, as well as external beam techniques including 3-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and proton therapy [5]. Over the past decade, 7 prospective randomized trials evaluating PBI have been presented, demonstrating low rates of local recurrence with PBI with no statistically significant differences in local recurrence in the majority of the trials (Table 2).

The initial modern technique evaluated to deliver PBI was interstitial brachytherapy; interstitial brachytherapy involves placing multiple catheters/needles in and around the lumpectomy cavity through the skin. The Hungarian National Institute of Oncology randomized trial evaluated PBI (delivered with interstitial brachytherapy [36.4 Gy/7 fractions, twice daily] or electrons) compared to WBI and found that at 10 years there was no difference in local recurrence or survival with improved cosmetic outcomes with interstitial PBI [24]. This led to the Groupe Europeen de Curietherapie- European Society for Radiotherapy and Oncology trial which randomized more than 1,100 patients to interstitial PBI (32 Gy/8 fractions, twice daily; 30.1 Gy/7 fractions, twice daily; 50 Gy delivered with pulsed dose rate over 60–85 hours) or WBI. With more than 6 year follow-up, no difference in rates of local recurrence (1.4% PBI *v* 0.9% WBI) were noted and reduced late skin toxicity was noted with interstitial PBI [25,26]. Drawbacks of interstitial brachytherapy include the technical complexity and therefore the limited number of centers that perform the procedure and the invasive nature of the procedure, which requires a procedure and may have associated discomfort.

External beam radiation therapy (EBRT) represents an alternative to brachytherapy based PBI with 4 randomized trials evaluating EBRT PBI (Table 2) [27-31]. The RAPID (Randomized trial of accelerated PBI using 3D-CRT) trial evaluated EBRT PBI delivered with 3D-CRT (38.5 Gy/10 fractions, twice daily) as compared to WBI. Interim analysis demonstrated increased rates of adverse cosmesis with PBI and rates of Grade 1–2 toxicity at 3 years [27]. Long-term data has recently been presented and with more than 8 year follow-up, no difference in rates of ipsilateral breast tumor recurrence were noted (3.0% PBI *v* 2.8% WBI. While associated with less acute toxicity, PBI was associated with increased late normal toxicity and worse cosmetic outcomes [28]. More recently, IMRT has been utilized to deliver external beam PBI. The University of Florence randomized trial included 520 women randomized to PBI (30 Gy/5fractions, every other day) or WBI. With 5 year follow-up, no difference in rates of local recurrence were noted (1.5% in both arms) with reduced acute/chronic toxicities and improved cosmesis in the PBI arm [29]. Similarly, the IMPORT (Intensity Modulated Partial Organ Radiotherapy)- LOW trial evaluated PBI (40 Gy/15 fractions, once daily) as compared to WBI (40 Gy/15 fractions or 36 Gy/15 fractions with boost to tumor bed). Outcomes demonstrated no difference in the rates of local recurrence, with PBI associated with reduction in breast firmness and changes in breast appearance [30].

Table 2
Randomized trials evaluating partial breast irradiation.

	NIO	GEC-ESTRO	RAPID	Florence	IMPORT LOW	Barcelona	NSABP B39
Number of patients	258	1,184	2,135	520	2,018	102	4,216
Follow-up (years)	10.2	6.6	8.6	5.0	6.0	5.0	10.2
Age	Mean: 59	Mean: 62	Mean: 61		Median: 62	Mean: 67	
Technique dose/fraction	MIB (5.2 Gy X 7, BID)	MIB(4 Gy x 8, BID; 4.3 Gy X 7, BID; 50 Gy pulsed dose)	EBRT (3D-CRT) (3.85 Gy X 10, BID)	EBRT (IMRT) (6 Gy X 5, QOD)	EBRT (IMRT) (2.67 Gy X 25, qday)	EBRT (3D-CRT) (3.85 Gy X 10, BID)	MIB, Applicator, EBRT (3D-CRT) (3.4 Gy X 10, BID-brachytherapy; 3.85 Gy X 10, BID)- EBRT
T-stage	T1 100%	T1 89%	61% < 1.5 cm	T1 94%	Median 1.2 cm	T1 92%	–
Estrogen receptor negative	8%	19%	10%	4%	5%	4%	19%
Node positive	2% (N1mic)	1% (N1mic)	0%	7.3%	2%	0%	10%
Endocrine therapy	69%	87%	69%	64%	91%	98%	–
Chemotherapy	2%	10%	15%	1.5%	7%	2%	29%
Local recurrence	5.9%	1.4%	3.0%	1.5%	1%	0%	4.8%

Abbreviations: NIO = National Institute of Oncology; GEC-ESTRO = Groupe Europeen de Curietherapie- European Society for Radiotherapy and Oncology; IMPORT = intensity modulated partial organ radiotherapy; NSABP = National Surgical Adjuvant Breast and Bowel Project; MIB = multicatheter interstitial brachytherapy; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; 3D-CRT = 3-dimensional conformal radiation therapy; BID = twice daily; QOD = every other day; qday = daily.

Table 3
Guidelines for patient selection for partial breast irradiation.

	ASTRO	ABS	ASBS	GEC-ESTRO
Age	≥ 50	≥ 45	≥ 45	≥ 50
Tumor size	≤2 cm	≤3 cm	≤3 cm	≤3 cm
Estrogen receptor	Positive	Positive/Negative	–	Any
Nodal status	Negative	Negative	Negative	Negative
LVSI	Not present	Not present	–	Not present
Histologies	Invasive ductal/favorable, DCIS ≤2.5 cm, ≥3 mm	All invasive, DCIS	All invasive, DCIS	Invasive ductal, mucinous, tubular, medullary, and colloid
Margins	Negative (≥2 mm)	Negative (no tumor on ink for invasive, ≥2 mm for DCIS)	Negative (no tumor on ink for invasive, ≥2 mm for DCIS)	Negative (≥2 mm)
Other	BRCA ½- negative Unifocal EIC negative		Multifocal ok if ≤3 cm total Focal LVI No genetic mutations	Unifocal

Abbreviations: ASTRO = American Society for Radiation Oncology; ABS = American Brachytherapy Society; ASBS= American Society of Brest Surgeons; GEC-ESTRO = Groupe Europeen de Curietherapie- European Society for Radiotherapy and Oncology; LVSI = lymphovascular space invasion; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component.

Recently, results of National Surgical Adjuvant Breast and Bowel Project B-39/RTOG 0413 were presented. The trial allowed for PBI to be delivered with interstitial brachytherapy, applicator brachytherapy (both at 34 Gy/10 fractions, twice daily), or with 3D-CRT PBI (38.5 Gy/10 fractions, twice daily, 71% of PBI patients). At 10 years, the ipsilateral breast tumor recurrence free rate was 95.2% with PBI and 95.9% with WBI, which despite being less than a 1% difference at 10 years, did not meet the statistical significance for equivalence as the 90% confidence interval was 0.94–1.58 and the study required it to be between 0.667 and 1.5. No differences in distant disease free interval, disease free survival, or overall survival were noted though increased grade 3 toxicities (9.6% *v* 7.1%) with PBI were identified [32]. Cosmetic outcomes from the study demonstrated equivalent outcomes between PBI and WBI when evaluated by patients [33]

At this time, multiple evidence-based guidelines exist to provide clinicians with recommendations for patient selection for PBI (Table 3) [4,5,34,35]. Additionally, the recent American Brachytherapy Society guidelines have provided recommendations regarding PBI techniques with strong recommendations for interstitial brachytherapy and IMRT and moderate recommendations for 3D-CRT and applicator brachytherapy [5].

Currently, research is underway evaluating shorter courses of PBI. The TRIUMPH-T (Tri-Fraction Radiothearpy Utilized to Minimize Patient Hospital Trips: a Phase II Trial) trial evaluated a 3-fraction brachytherapy regimen delivered with applicators (7.5 Gy X 3 fractions). Two hundred patients were enrolled, and with a minimum follow-up of 6 months, low rates of grade 3 toxicity were noted with 97% excellent/good cosmetic outcomes [36]. Showalter et al has also recently presented an initial study evaluating a single fraction perioperative approach with further studies underway [37]. With respect to external beam radiation PBI, initial 1-year results of the ACCEL (Accelerated Partial Breast Irradiation Using 5 Daily Fractions: A SIngle-Arm, Phase II, Prospective Cohort Study to Examine Cosmetic Outcomes and Toxicity) trial demonstrated acceptable 1-year cosmesis and no grade 2 fibrosis with continued accrual planned [38]. Finally, studies have emerged evaluating the role of preoperative PBI, primarily as a single fraction, with promising short-term results and larger studies underway [39].

Intraoperative radiation therapy

IORT represents a technique that has the opportunity to offer patients the ability to complete both their surgery and adjuvant radiation therapy in a single treatment. Multiple IORT techniques exist including low-energy x-rays, electrons, and high dose rate brachytherapy [40]. At this time, 2 randomized trials have been published evaluating the role of IORT in the management of early stage breast cancers. The TARGIT-A trial utilized low-energy x-rays and randomized 3,451 patients to IORT (either delivered at the time of initial surgery or as a second procedure, ie, delayed IORT or post-pathology) or WBI. Overall, 15% of patients received supplemental WBI in the IORT

arm. The trial was published with short follow-up (29 months), with 5-year local recurrence rates increased with IORT (3.3% *v* 1.3%), though it was within the non-inferiority margin. The delayed post-pathology cohort had an increased rate of local recurrence with IORT (5.4% *v* 1.7%) [41]. Of note, the results of this study raised significant concerns regarding statistical methodology, short follow-up, and conclusions drawn by the study [42,43].

A second randomized trial (ELIOT - Electron Intraoperative Radiation Therapy) evaluated the role of electron IORT compared to WBI in 1,305 women with no additional WBI given. At 5 years, IORT was associated with increased rates of local recurrence (4.4% *v* 0.4%); inclusion of non-suitable and higher risk patients (age < 50, node positive, estrogen negative) and lack of whole breast irradiation for higher risk patients may have impacted these outcomes [44]. However, analysis of good risk patients (as defined by the Groupe Europeen de Curietherapie- European Society for Radiotherapy and Oncology guidelines) did demonstrate low rates of local recurrence [45]. One key concern with IORT is that with relatively short follow-up, higher rates of local recurrence have been seen, which is inconsistent with the results of PBI techniques such as interstitial brachytherapy, applicator brachytherapy, or external beam. As such the American Society for Radiation Oncology PBI guidelines recommend low-energy IORT to be used on prospective study only and electron IORT for suitable risk patients only, while the American Brachytherapy Society PBI and IORT guidelines recommend IORT be limited to prospective study alone. [4,5,40].

De-intensification of treatment

Initial trials evaluating breast-conserving therapy consisted of breast conserving surgery followed by adjuvant WBI [1,8-10]. Early studies evaluating the omission of adjuvant radiotherapy following breast conserving surgery identified significantly higher rates of local recurrence as well as the potential for worse disease free survival [46,47]; a meta-analysis found that the omission of radiation therapy not only impacted local recurrence but also negatively impacted breast cancer mortality [1]. More recently, studies have looked at the omission of adjuvant radiation therapy in lower risk patients. Cancer and Leukemia Group B (CALGB) 9343 evaluated patients 70 years or older with T1N0-x breast cancers undergoing breast conservation; patients were randomized to tamoxifen or tamoxifen with WBI and at 10 years the omission of radiation therapy was associated with an increase in local recurrence (10% *v* 2%), with no impact on survival [6]. Similar studies have evaluated low-risk patients and found similar results with shorter follow-up [7,48]. With respect to patients with ductal carcinoma in situ (DCIS), similar findings to studies of invasive cancers were seen in RTOG 9804 [49]; however, the ECOG 5194 prospective trial demonstrated 12 year local recurrence rates of 14.4%/24.6% for low-intermediate/high grade disease with no plateau noted in recurrences [50]. Similarly, an update from the Dana-Farber DCIS trial found a 13% local recurrence rate at 8 years and 15.6% at 10 years [51].

While previous studies have evaluated patient, clinical, and pathologic factors to determine eligibility for treatment de-intensification, growing data support the use to tumor biology and genetics to help in evaluating patients for de-intensification. Liu et al evaluated the impact of radiation therapy by breast cancer subtype and found that luminal A and B subtypes benefit less than high risk subtypes, with no different in ipsilateral breast recurrence at 10 years for luminal A breast cancer patients based on receipt of radiation therapy (RT) [52]. At this time, multiple studies are underway evaluating the omission of radiation therapy for low-risk luminal A breast cancer patients with outcomes expected in the years to come.

Over the past 2 decades, the role of tumor genetics has redefined how systemic therapy decisions are made [53]. Currently, studies are underway evaluating the role of such techniques in radiation therapy decisions with invasive cancers as well as DCIS [52-55]. Initial work utilizing tumor genetics (Oncotype DX DCIS Score) to identify a low-risk cohort of patients with DCIS who may not require radiation has identified low-risk cohorts with local recurrence rates similar to those determined to be low-risk based on clinical and pathologic features [55,56]. However, recent data has demonstrated a potentially different approach (DCISionRT) to identifying low-risk DCIS patients with future studies required to evaluate clinical outcomes by genomic profile risk [57].

While most de-intensification studies have focused on omitting radiation therapy for low-risk hormone-receptor positive breast cancers, growing discussions have emerged regarding replacing endocrine therapy alone following breast conserving surgery with radiation therapy alone. This is based on data demonstrating low long-term compliance with endocrine therapy, while radiation therapy has been associated with high compliance and the potential for reduced or altered toxicity profiles [58,59]. A microsimulation analysis from Ward et al found comparable outcomes and costs with radiation alone compared to endocrine therapy alone in a population of patients similar to CALGB 9343 [60]. A National Cancer Database analysis of 2,295 women 70 years or older with T1N0, hormone receptor positive, HER2 negative breast cancer undergoing lumpectomy found equivalent 5 year survival [61]. Moving forward, randomized trials evaluating this concept are anticipated.

Regional nodal irradiation/axillary management

Over the past few years, the role of RNI has been redefined. Traditionally, most patients undergoing radiation therapy following mastectomy, ie, postmastectomy radiation therapy (PMRT), have had radiation therapy treatment fields that include RNI (supraclavicular, axilla, internal mammary nodes) based on randomized trials evaluating the role of PMRT [62-64]. Following breast conserving surgery, the role of RNI was unclear with RNI recommended for patients with 4 or more nodes involved, with controversy regarding RNI for patients with 1-3 involved nodes. However, recent trials have provided clarity regarding the role of RNI. The MA-20 trial randomized 1,832 women following breast-conserving surgery to adjuvant WBI or WBI with RNI (supraclavicular, axillary, internal mammary). The majority of women in both arms had 1-3 nodes involved (approximately 85% of patients in each arm) with 10% of patients having high-risk node negative disease following axillary dissection and approximately 85% of patients receiving anthracycline chemotherapy (25% with taxane). At 10 years, the addition of RNI was associated with a significant improvement in disease free survival (82% *v* 77%), distant disease free survival (86.3% *v* 82.4%), and locoregional disease free survival (95.2% *v* 92.2%); while no overall survival advantage was noted, a survival advantage was noted for estrogen receptor negative patients (81.3% *v* 73.9%), in a preplanned subset analysis. RNI was associated with low rates of toxicity with a 1% increase in pneumonitis and 4% increase in lymphedema, with no difference in cardiac toxicities [65]. Similarly, the EORTC 22922 randomized trial included 4,004 patients (76% undergoing BCT) with patient randomized to no RNI or RNI directed to the internal mammary and medial supraclavicular nodes. At 10 years, a trend for improved survival (82.3% *v* 80.7%, $P = 0.06$) was noted with the addition of RNI with improvements in disease free survival (72.1% *v* 69.1%), distant disease free survival (78% *v* 75%), and breast cancer mortality (12.5% *v* 14.4%). Toxicity increases were modest with the addition of RNI [66]. Taken together, these data support the utilization of RNI in patients with

limited nodal involvement with improvement in clinical outcomes and small increases in acute and chronic toxicities.

While all the aforementioned studies included internal mammary radiation (IMN RT), controversy has existed regarding the role of IMN RT with previous studies failing to demonstrate a benefit [67,68]. However, data from the MA20 and EORTC 22922 trials has supported the addition of IMN RT when treating with RNI [65,66]. Additionally, a study from Thorsen et al evaluated the role of IMN RT; 3,089 patients in a prospective population-based cohort study were evaluated, with right-sided breast cancer patients undergoing IMN RT and left sided patients not undergoing IMN RT (due to concerns regarding radiation induced cardiac toxicity). With 8.9 year follow-up, the additional of IMN RT improved overall survival (75.9% *v* 72.2%) [69]. The results of these findings support the role of IMN RT in cases where pulmonary and cardiac dose constraints can be met.

In patients found to have positive sentinel lymph nodes at surgery, the standard of care has been axillary lymph node dissection (ALND). However, the ACOSOG Z011 and AMAROS trials have demonstrated that the omission of ALND is safe in appropriately selected patients with positive sentinel nodes. As there was heterogeneity in radiation field design in these trials, radiation fields can be targeted based on the omission of ALND, with the use of tangent-only radiation therapy, high tangent radiation, or RNI based on patient, clinical, and pathologic factors [70-72]. While the majority of patients in these studies underwent breast-conserving surgery, it is appropriate to translate the findings of these studies to appropriate patients undergoing mastectomy with positive sentinel lymph node biopsy [73].

Postmastectomy radiation therapy

As noted above, multiple randomized trials have demonstrated a reduction in locoregional recurrences and improvement in survival with the addition of PMRT in appropriately selected patients (tumors greater than 5 cm [T3–T4 disease], nodal positivity, or positive margins) [62-64]. Traditionally, PMRT has been delivered over 5 weeks, encompassing the chest wall and regional nodes. However, similar to whole breast irradiation, studies have evaluated the role of hypofractionated PMRT. A randomized trial of 820 patients evaluated hypofractionated PMRT compared to standard PMRT and found no difference in rates of locoregional recurrence (8.3% hypofractionated PMRT *v* 8.1% standard PMRT) with no significant difference in acute and late toxicities (reduction in grade 3 acute skin toxicity with hypofractionated PMRT) with 5-year follow-up [74]. Long-term outcomes from the subset of patients on the START trial that had hypofractionated RNI demonstrated safety with respect to arm and shoulder symptoms [75]. One concern regarding hypofractionated PMRT has been in patients undergoing reconstruction and the potential for increased reconstruction toxicities. Khan et al published results from a prospective study evaluating hypofractionated PMRT (36.63 Gy/11 fractions); 69 patients were enrolled and at 32 month follow-up, no grade 3 toxicities were noted, however, 24% of patients experienced implant loss or failure, and 8% had to undergo unplanned surgical correction (32% total complication rate) [76]. Currently, a national multiinstitutional randomized trial (RT CHARM Phase III Randomized Trial of Hypofractionated Post Mastectomy Radiation With Breast Reconstruction) is underway evaluating the role of hypofractionated PMRT in patients undergoing reconstruction following mastectomy [77].

Traditionally, PMRT has been given to patients based on TNM staging with common indications being tumors greater than 5 cm (T3–T4 disease), nodal positivity, or positive margins. However, recent data has suggested that tumor biology should be part of the discussion with respect to PMRT, particularly for patients with triple negative breast cancer [78,79]. Recent studies have supported the role of adjuvant radiation therapy with reductions in locoregional recurrences and improvements in survival [80,81]; however, further data with long term follow-up is required before PMRT should be offered to such patients off study.

Oligometastatic breast cancer

Metastatic disease has been felt to be a binary state for decades, defined by simply the presence or absence of distant disease involvement. However, more recently, concepts of oligometastatic disease, where limited numbers of metastatic foci are present, and oligoprogressive disease, where a limited number of foci have progressed, have joined the clinical lexicon.

In patients with metastatic breast cancer, several studies have evaluated the role of mastectomy with mixed results [82,83]. At this time, there are no firm indications for mastectomy in patients with metastatic disease but radiation can be considered for palliation, in cases with limited metastatic disease where definitive therapy is planned, or in cases where metastatic disease has responded or been stable for some time. Additionally, for patients with metastatic cancers with oligometastatic disease (including breast cancer), stereotactic body radiation therapy (SBRT) to metastatic sites has been evaluated [84,85]. The SABR COMET trial was an open-label phase 2 study evaluating the role of SBRT. In total, 99 patients were included (including 18 patients with breast cancer); with 25-month follow-up, median survival was 28 months without SBRT and 41 months with SBRT ($P = 0.09$), though there was a 4-5% risk of treatment related death [86]. Recently, the NRG BR-001 trial closed; this phase I study evaluated SBRT for multiple metastases with initial outcomes demonstrating no prespecified-dose limiting toxicities [87]. Currently, NRG BR-002 is accruing which is a phase II/III trial evaluating SBRT/surgical resection to all metastatic sites in newly diagnosed patients with oligometastatic breast cancer who have received 12 months of 1st line systemic therapy without progression [88]. With respect to patient selection criteria, this is an evolving area of study with a lack of consensus on patient eligibility at this time; however, NRG BR-002 inclusion criteria consist of patients with biopsy confirmed metastatic breast cancer with 4 or fewer metastatic lesions (Sites: lung, bone/spine, liver, mediastinal/cervical nodes, and abdominal/pelvic nodes or adrenal gland). All lesions must be amenable to SBRT or resection and the maximum size of a lesion is 5 cm.

Discussion

While radiation therapy has been a standard of care component in the treatment of breast cancer, novel radiation therapy approaches continue to redefine treatment options for patients. In patients with DCIS and early stage invasive breast cancers, the most commonly used approach has been standard WBI since the inception of BCT. However, the 6–7 weeks of WBI has been replaced by HWBI in most cases, reducing treatment duration in half [3]. With multiple level I sources of evidence and national guidelines available, HWBI must be adopted more consistently, as current studies have demonstrated poor adoption of the technique [89]. With rising costs of breast cancer care, adopting HWBI represents an evidence based value approach to managing breast cancer [90] Additionally, for patients with DCIS and early stage breast cancers, growing data supports the use of PBI, which can not only reduce treatment to 1–3weeks, but also offer the potential for less side effects. Similar to HWBI, PBI approaches can represent a cost saving option for patients and payers, providing value based approaches [91,92].

For patients with sentinel node positive disease meeting inclusion criteria level I evidence supports the omission of axillary dissection, reducing toxicities including lymphedema, with no differ-

ence in rates of locoregional recurrence or survival. Additionally, for patients with limited nodal disease, trials now support the benefit of adding RNI with reductions in locoregional recurrence and distant metastases as well as the potential for survival advantages in certain subsets. While there may be subsets of patients who do not demonstrate consistent benefits to RNI, these populations have not yet been elucidated and further studies are required to identify which patients with limited nodal disease can forgo RNI. In the interim, RNI should be considered for all patients with limited nodal burdens.

As hypofractionation has become standard for DCIS, and early stage breast cancers, growing data supports the role of hypofractionation for intact breast cancer with RNI, as well as cases of non-reconstructed chest walls following mastectomy. In the years to come, data is expected on outcomes of hypofractionated radiation therapy in reconstructed chest wall cases, again offering the potential to reduce treatment duration and improve the value proposition of breast radiotherapy.

The utilization of radiation in therapy for metastatic breast cancer has expanded beyond palliation to include definitive treatment. Studies are currently underway in order to best define which patients should be treated with oligometastatic intent, as well as the best techniques to treat primaries as well as metastatic sites.

Conclusions

Radiation therapy approaches in breast cancer continue to evolve with novel options now available for clinicians. In early stage breast cancers, HWBI is standard of care with shorter courses being evaluated. PBI has emerged as a standard approach for appropriately selected patients with studies evaluating the role of tumor biology and genetics in omitting radiation therapy. Locally advanced breast cancers represent an area where hypofractionated regimens are being evaluated as well. Finally, oligometastatic breast cancer represents an emerging field, with the use of techniques such as stereotactic body radiation therapy offering definitive treatment for limited metastatic disease.

Conflict of interest

Chirag Shah- Consultant, Impedimed; Travel/Grants, Varian Medical Systems; Grant- Vision RT; Grant- PreludeDx; Kristine Bauer-Nilsen- None; Ryan Hard- None; Frank Vicini- Chief medical officer, Impedimed.

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