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LOCAL-REGIONAL EVALUATION AND THERAPY (A KONG, SECTION EDITOR)

Advances in Breast Cancer Radiation Therapy

Michael Siedow[1] · Valerie Grignol[2]

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Abstract

Purpose of Review Radiation therapy remains an integral component in the treatment of all stages of breast cancer which is the leading cause of cancer worldwide for women. We aimed to identify and characterize clinical trials in radiation therapy that have led to changes in practice essential for every physician who treats breast cancer.

Recent Findings Hypofractionation, accelerated partial breast irradiation, and prone positioning have led to shorter treatment times and decreased toxicity for early-stage breast cancer patients. For patients with nodal metastasis, regional nodal radiation has improved disease-free survival and local recurrence in most breast cancer subtypes. The role of radiation in metastatic disease is transitioning from palliation alone to ablative therapy in patients with oligometastatic disease.

Summary Radiation therapy remains a pillar in the management of breast cancer. Research published since 2015 has established new standards of care in the delivery of radiation therapy to breast cancer patients. Ongoing trials and future work seek to evaluate who benefits most, whom therapy can be avoided, and the expanding role in definitive treatment of metastatic disease.

Keywords Accelerated partial breast irradiation (APBI) · Breast cosmesis · Hypofractionated radiation therapy · Oligometastatic breast cancer · Prone positioning · Regional nodal irradiation (RNI)

Introduction

Radiation as an adjunct to surgery for the treatment of breast cancer has been utilized since its discovery. Breast cancer remains the most frequently diagnosed and leading cause for cancer-related death in women worldwide [1]. Widespread use of radiation therapy for the treatment of breast cancer began when radiotherapy was shown to improve local recurrence rates as part of breast conservation as well as survival in patients with lymph node metastasis after mastectomy [2]. Radiation has been shown to have an integral role in the treatment and management of every stage of breast cancer. Sentinel studies published in the last 5 years have demonstrated advances in radiation therapy that are more targeted, convenient, and less toxic to patients while improving clinical outcomes. In our review, we analyzed recent literature and large randomized clinical trials in the USA and abroad shaping the field of radiation oncology and changing the management of early-stage, locally advanced, and oligometastatic breast cancer.

This article is part of the Topical Collection on *Local-Regional Evaluation and Therapy*

✉ Valerie Grignol
valerie.grignol@osumc.edu

[1] Department of Radiation Oncology, The Ohio State University, Columbus, OH, USA

[2] Department of Surgery, Division of Surgical Oncology, The Ohio State University, 410 W. 10th Ave, Columbus, OH, USA

Early-Stage Breast Cancer

The treatment of early-stage breast cancer is surgical resection followed by adjuvant therapy consisting of chemotherapy, radiation therapy, and endocrine therapy determined by breast cancer subtype and extent of disease. With the advent of breast conservation techniques in the 1980s, radiation therapy has been a mainstay in the treatment of breast cancer over the past 30 years. Breast conservation techniques known as lumpectomy or partial mastectomy remove the tumor with a margin of normal tissue thereby preserving the majority of breast tissue. In-breast recurrence rates are similar to mastectomy when adjuvant radiation is performed after resection [3]. The initial technique of 50 Gy in 25 fractions delivered to the whole breast following lumpectomy became firmly solidified as the

standard of care (SOC) after 17 randomized trials with more 10,000 patients demonstrating its benefit [4]. In 2010, Whelan et al. published the results of OCOG 93-101, followed 3 years later by the UK Standardisation of Breast Radiotherapy (START) trials in 2013 comparing standard fractionation (2 Gy daily) versus hypofractionated regimens consisting of 40 Gy in 15 fractions (266 cGy daily). Long-term results have shown hypofractionation to be equivalent with the historical SOC with no difference in local recurrence (LR), cosmesis, grade 3 skin toxicity, disease-specific survival (DSS), or overall survival (OS) [5]. Hypofractionated whole-breast radiation is safe, effective, and has become the new SOC in the treatment of early-stage breast cancer. Despite being a considerable improvement, drawbacks remain. Three weeks of treatment is still problematic for women who do not live near radiation therapy facilities, have socioeconomic barriers, work full time, or need childcare [5].

Accelerated Partial Breast Irradiation

Advances in technology, re-evaluation of central breast cancer radiobiology tenets and the development of breast cancer subtypes have all supported the growth and widespread use of accelerated partial breast irradiation (APBI) in modern radiation oncology. In contrast with conventional whole-breast irradiation (WBI), APBI treats only the lumpectomy cavity and a small clinical target volume (CTV) encompassing microscopic disease. A retrospective review of NSABP B-06 found the majority (> 80%) of in-breast tumor recurrences (IBTR) occur within 2 cm of the post-excision lumpectomy cavity providing the basis to target the lumpectomy cavity alone rather than treating the whole breast [6]. Integration of advanced imaging technology into linear accelerators has allowed radiation oncologists to accurately and reproducibly locate and treat the lumpectomy cavity on a daily basis. Four large, randomized trials published in the last 7 years, NIO Budapest, University of Florence, GEC-ESTRO, and OCOG Rapid all found local regional recurrence (LRR) rates to be non-inferior to WBI as seen in Table 1 [7–10]. In contrast, preliminary results from NSABP B-39/RTOG-0413 published in December 2019 found WBI superior to APBI [11]. Cumulative 10-year rates of IBTR were 4.6% and 3.9% with APBI and WBI, respectively in this study. With a hazard ratio (HR) of 1.22 (90% CI 0.94–1.58), the study did not meet the pre-specified limits for equivalence (HR range 0.667–1.5), thus favoring WBI. This study is the first and only trial to demonstrate an advantage for WBI. A notable difference between NSABP B-39/RTOG-0413 and the four preceding trials is its broad and heterogeneous patient population (Table 2). Median age, ER/PR status, grade, percent DCIS, invasive cancer, and nodal involvement all differed significantly in B-39/RTOG-0413 compared with the other patient cohorts [11]. Although it did not meet "non-inferior" criteria, the absolute difference was less than 1% in the 10-year incidence of IBTR when comparing APBI with WBI. This absolute difference of less than 1% led the authors to conclude ABPI is an acceptable alternative for women with early-stage breast cancer with the notable exception of non-luminal histologies and women who will not undergo hormone therapy [11]. Further clinical trials looking at these higher-risk subgroups are warranted, but APBI appears to be a highly effective and convenient option for a large number of women with early-stage breast cancer.

Cosmetic Outcomes and Adverse Events in APBI

Critics of APBI have raised concerns regarding breast cosmesis given the larger dose per fraction, abbreviated treatment times, and lack of long-term clinical trial outcomes. With a median follow-up of more than 10 years, B-39/RTOG-0413 found equivalent cosmetic outcomes between ABPI and conventional fractionation, with no difference at 1 and 3 years in global cosmetic scores, encompassing both patient and physician grades [12]. Similarly in OCOG-RAPID and GEC-ESTRO, APBI produced excellent cosmetic outcomes compared with whole-breast regimens. In addition to equivalent cosmesis, ABPI was also well-tolerated with manageable toxicity profiles. In B-39/RTOG-0413, 97% of the 4216 patients

Table 1 Randomized phase 3 trials comparing APBI to WBI

				Local recurrence (%)		Regional recurrence (%)	
Clinical Trial	*n*	Median follow-up (years)	APBI method	APBI	WBI	APBI	WBI
NSABP B39-RTOG 0413	4216	10.2	3D-CRT or Brachy	4.6	3.9	-	-
RAPID	2135	8.6	3D-CRT	3	2.8	0.4	0.2
GEC-ESTRO	1184	6.6	Brachy	1.44	0.92	0.48	0.18
Florence	520	5.0	IMRT	1.5	1.5	1.4	1.9
Hungary	258	10.2	Brachy	5.9	5.1	2.5	1.7

Table 2 Patient characteristics in APBI trials

Clinical trial	*n*	Follow-up (years)	Median age (years)	Patients ER+/PR+ (%)	Grades 1–2 (%)	DCIS (%)	T1 (%)	N0 (%)
NSABP B39-RTOG 0413	4216	10.2	54	81	65	24	86	90
RAPID	2135	8.6	61	90	83	18	-	99
GEC-ESTRO	1184	6.6	62	92	90	5	89	100
Florence	520	5.0	62	96	89	11	93	86
Hungary	258	10.2	–	89	100	0	100	94

enrolled reported adverse event information. Ten percent of APBI patients reported grade 3 toxicities versus 7% with WBI. Less than 1% of patients reported grade 4 or 5 toxicities in both arms. Clinically manageable grade 1 and grade 2 toxicities were found to occur in 40% and 44% of the APBI and WBI cohorts. With long-term follow-up in multiple randomized clinical trials, APBI has been proven to be well-tolerated and has excellent cosmetic outcomes in women with early-stage breast cancer.

APBI Guideline Updates

In March 2017, ASTRO published consensus guidelines updating the original 2009 statement regarding which patients were suitable for APBI based on published evidence and expert opinion. Notable updates included lowering the "suitability" age from 60 to 50 years old with a "cautionary" group for women 40 years or older who met all other criteria. The expert panel made several notable changes regarding intraoperative radiotherapy (IORT) as well and recommended its use only in women with invasive cancer who are 50 years or older and have Tis or T1 disease with negative margins. The guidelines recommended patients be counseled regarding the higher rate of IBTR in patients treated with IORT compared with WBI and the need for monitoring of long-term local control and toxicity given limited follow-up. The expert panel made no change to margin status recommending they be negative by at least 2 mm.

Prone Positioning

Prone patient positioning (face down) has become an increasingly popular method of radiation delivery over the past decade to minimize long-term treatment-associated morbidity in woman with early-stage disease. A SEER analysis of more than 300,000 women with early-stage breast cancer over a 30-year period identified higher cardiac and lung cancer mortality, particularly in patients treated in the 1970s with older methods of radiation planning and patient positioning [13]. It became evident from early work in the late 1990s that treating patients in the prone position may be a way to minimize cardiac and pulmonary toxicity in patients with advanced COPD or heart conditions. With the patient in a prone position, the breast falls naturally through the treatment table. Working with a trained dosimetrist an external beam treatment plan can be created to maximize dose to the planned tumor volume (PTV) and minimize dose to the ipsilateral lung and heart. Dosimetrically, prone setup decreases skin toxicity, lowers heart dose, particularly on left-sided cases, reduces lung dose and chest wall motion, and creates a more homogenous dose distribution [14]. High-volume centers have shown an improvement in lung V20 (volume receiving at least 20 Gy) of 10% on a consistent basis when using prone positioning. However, setup and reproducibility can be challenging, patients may be on the treatment table for long periods of time, and additional on-board imaging is necessary before treatments are delivered. Multiple large institutions have shown women with a BMI > 35 and those who have large pendulous breasts tend to have better cosmetic outcomes, lower incidence of moist desquamation, grade 2 mastalgia, and dermatitis when treated prone [15]. One major barrier to widespread implementation of prone therapy is the time and resources required to equip and train radiation therapists which limits its feasibility outside of high-volume centers with a large breast cancer patient population. The number of large academic centers and even community practices implementing prone positioning has grown over the past 10–15 years in step with the implementation of APBI.

Deep Inspiration Breath Hold

Treatment of left-sided breast cancers and internal mammary lymph nodes (IMNs) with radiation therapy carries a higher risk of cardiac toxicity given their anatomic relationship. Darby et al. showed a 7.4% increase in the risk of a major cardiac event (myocardial infarction, coronary revascularization, or death from ischemic heart disease) per gray of mean heart dose received in a study of 2168 patients who completed radiation therapy from 1958 to 2001 [16]. The delivery of radiation has made significant strides since 1958; nevertheless, this study showed any reduction in mean heart dose is beneficial to the patient. Deep inspiration breath hold (DIBH) is a respiratory gating technique during a specific window of the inspiratory cycle utilized when radiation is delivered to left breast tumors and regional nodes. The patient is coached by the radiation therapist during treatment to breathe in a reproducible, steady

cadence. A trial of 272 patients with left-sided breast cancers found DIBH treatments were feasible in 79% of patients in which it was attempted [17]. In the same study, DIBH plans reduced the V13 (volume receiving at least 13 Gy) to the heart by 80% (median 1.39 to 0.24 Gy, $p = 0.032$) compared with standard free-breathing techniques. Ipsilateral lung dose was elevated in the DIBH treatment group, 8.4 Gy compared to 6.64 Gy; however, this difference was not statistically significant ($p = 0.63$) [17]. In 2017, a nationwide survey found that DIBH was the most common heart-sparing technique and was utilized in 83% of all practices [18].

Treatment of Locally Advanced Disease

Regional Nodal Irradiation

Regional nodal irradiation (RNI) consisting of radiation therapy to the chest wall and regional lymph nodes (supraclavicular, axillary, and internal mammary per NRG guidelines) is commonly used in the adjuvant setting in women with node-positive breast cancer following mastectomy [19, 20]. The sentinel work by Ragaz et al. published in NEJM in 1997 showed women with early-stage breast cancer who were found to be pathologically node-positive after mastectomy/axillary lymph node dissection (ALND) had a statistically significant improvement in OS, disease-free survival (DFS), and local regional recurrence (LRR) at 20 years. Most notable from this study was a paradigm shifting 10% improvement in OS from 37 to 47% ($p = 0.03$) with the addition of RNI to post-mastectomy radiation therapy (PMRT) [19]. Overgaard published the Danish Breast Cancer Cooperative Group 82b evaluating PMRT and CMF (cyclophosphamide, methotrexate, fluorouracil) ±RNI and reported a 9% improvement in OS at 10 years and similar improvements in locoregional recurrence (LRR) and disease-free survival (DFS) [20]. These trials provided level-one evidence that established the use of PMRT and RNI following mastectomy. Criticisms of these trials included the fact that the number of nodes removed with an ALND was well below today's standards (average 7–11 in both trials), the control arms had notably high rates of local recurrence, and chemotherapy regimens lacked anthracyclines and taxanes. Nonetheless, regional nodal irradiation clearly improved overall survival in this population.

RNI and Breast Conservation

In 2015, the results of the MA.20 trial were published which evaluated RNI and WBI in women treated with lumpectomy alone who were pathologically node-positive or had high-risk features (tumor > 5 cm OR tumor > 2 cm with fewer than 10 LN removed AND at least one of the following: grade 3 histology, ER negativity, and LVSI). With a median follow-up of 9.5 years, there was a statistically significant difference in DFS, local regional DFS, distant DFS, and breast cancer mortality (BCM), but not OS (Table 3). RNI was associated with higher rates of pneumonitis (0.2 versus 1.2%, $p < 0.001$) and lymphedema (4.5 versus 8.4%, $p < 0.001$) [21]. These results were mirrored in EORTC 22922, which included more than 4000 women with axillary LN-positive tumors or medial primary tumors (central tumors ± node positive) who were randomized to whole-breast irradiation ± RNI. Similar trends were seen in LRR, DFS, and distant DFS ($p = 0.06$) and a trend toward an improvement in OS (80.7% versus 82.3%) in the RNI cohort [21]. Of note, treatment plans from EORTC 22922 omitted the IMNs/medial supraclavicular nodes, and only 8.3% of the RNI group had their axillary nodes irradiated. This finding differed from MA.20 where all patients randomized to RNI had these areas treated within the pre-defined RNI target volume. Patient populations differed as well. Nearly half the patients on EORTC 22922 were node-negative and 90% were considered "low-risk" according the MA.20 criteria. Additionally, 25% received chemotherapy and 29% received hormone therapy, whereas 90% of patients enrolled on MA.20 received chemotherapy. Despite their differences, both EORTC 22922 and MA.20 clearly showed benefits in distant metastasis-free survival and DFS, and had strong trends for improved OS. Critics point out that although statistically significant, the absolute difference attributed to RNI is roughly 2–3% in terms of distant metastasis or disease-free survival in both these trials. RNI compared to WBI alone was associated with reducing an incurable metastatic state and a similar absolute difference of 2–3% in distant metastasis that is seen with the addition of other first-line therapies like tamoxifen and trastuzumab which are widely used in clinical practice.

Treatment De-escalation in Node-Positive Patients

The benefit of RNI following mastectomy and BCS in patients with multiple pathologically positive nodes is clear; however, its role is less understood in biologically low-risk patients with limited nodal disease. The Oncotype DX Recurrence Score (RS), a 21 gene recurrence score model, was found to predict LRR in node-positive breast cancer by the work of Mamounas et al. in 2017 [22]. These investigators looked at 1065 patients treated on NSABP-B28 and found on multivariate analysis adjusting for surgery and type of chemotherapy, RS was an independent predictor of LRR (HR = 2.86, 95% CI 1.51–5.31, $p = 0.008$). Patients with 1–3 positive nodes following lumpectomy had a LRR of 3.9%, 6.2%, and 10.5% for low, moderate, and high RS patients, and for patients treated with mastectomy, the risks were 2.4%, 4.1%, and 6.0% for the same RS categories. Pre-planned subgroup analysis from EORTC 22922 and MA.20 found that DFS following RNI was less beneficial in women with estrogen receptor (ER)–positive disease compared with those with ER-negative disease [21, 23].

Table 3 Randomized Phase 3 Trials evaluating RNI in addition to WBI

			Local regional DFS (%)			Disease-free survival (%)			Distant disease-free survival (%)		
Clinical trial	*n*	N1 (%)	WBI alone	WBI w/ RNI	*p*	WBI alone	WBI w/ RNI	*p*	WBI alone	WBI w/ RNI	*p*
EORTC 22922	4004	43	-	-	-	69.1	72.1	0.04	75	78	0.02
NCIC-MA.20	1832	85	92.2	95.2	0.009	77	82	0.01	82.4	86.3	0.03

Additional analysis from the same trials found for luminal A cancers that there was no effect of RNI (HR = 1.09, 95% CI 0.75–1.57) in contrast to luminal B breast cancers (HR = 0.66, 95% CI 0.460–0.94) and HER2-enriched or basal-like cancers (HR = 0.59, 95% CI 0.40–0.86, $p = 0.05$). These findings taken together provided the foundation for the Canadian Cancer Trials Group (CCTG) Trial MA.39, an ongoing randomized phase III non-inferiority trial in women 40 years or older with low-risk ER+ breast cancer with an Oncotype Recurrence Score < 18 undergoing mastectomy or breast conservation randomized to RNI versus observation. MA.39 opened with an accrual goal of 2140 patients in May 2018 with the goal of completing accrual by December 2027. The radiation oncology community expects the results of this trial to help guide clinical decision-making in these biologically low-risk patients with limited nodal metastases with respect to RNI.

Role of Axillary Lymph Node Dissection

In 2002, the long-term outcomes of NSABP B-04 were published demonstrating that no survival advantage was found in patients who had occult positive nodes removed during surgery [2]. With this in mind, ACOSOG Z0011 randomized patients with cT1-2N0 disease and 1–2 positive sentinel lymph nodes (SLN) at surgery to completion ALND or observation. All patients in this trial went on to receive WBI and systemic therapy. Results published in 2011 found no improvement in IBRT, nodal recurrence, DFS, or OS in patients who had completion ALND [24]. Of note, women randomized to ALND had an 11% increase in subjective lymphedema ($p \leq 0.0001$) and measurement of arm circumference. AMAROS/EORTC 10981/22023 was a non-inferiority trial randomizing 4806 patients with cT1-2N0 disease to RNI or completion ALND following a positive SLNB. The five-year results published in 2014 found no difference in OS or DFS. Similar to Z0011, a 14% increase in lymphedema ($p < 0.001$) was found in women randomized to ALND [25]. With the increased use of neoadjuvant chemotherapy, the role ALND and RNI is being investigated in patients who have a clinical response prior to surgery. ALLIANCE A11202 is an ongoing phase III trial in cT1-T3N1 patients evaluating the role of ALND and RNI in patients receiving neoadjuvant chemotherapy that have demonstrated clinical response in the lymph nodes to chemotherapy. In this study, patients are randomized to ALND and RNI alone if microscopic disease remains in the sentinel node(s) with the aim of demonstrating non-inferiority of RNI alone to ALND and RNI. With this goal of de-escalation in mind, NSABP B-51 randomizes cT1-T3N1 patients who convert to ypN0 after neoadjuvant chemotherapy to RNI versus observation. All patients enrolled must have a definitive surgery with negative axillary nodes through ALND or SLNB. Patients who underwent BCS receive WBI with or without RNI. Women undergoing mastectomy are randomized to PMRT or observation [26]. Together, these trials may support future efforts to de-escalate therapy and minimize comorbidities in the node-positive patient population.

Oligometastatic Breast Cancer

Metastatic breast cancer (MBC) presents as a spectrum of disease with patterns and outcomes strongly correlating with receptor status. Traditionally, MBC was managed primarily with systemic therapy, and radiation was reserved for palliation of symptomatic areas with five and ten fraction regimens. The concept of oligometastatic disease as it pertains to breast cancer was first established in the 1990s by Hellman and Weischelbaum [27]. Oligometastases or an oligometastatic state occurs when metastatic disease is localized to a limited number of sites and may be treated definitively in the appropriate setting. De Palma et al. published the results of the SABR-COMET trial in 2019 where patients were randomized 2:1 to receive stereotactic ablative radiotherapy (SABR) versus the standard of care palliative treatment in patients with one to five oligometastases. Results demonstrated that the addition of SABR resulted in a 13-month improvement in OS (28 versus 41 months, HR 0.57) and doubled the progression-free survival (6 versus 12 months, HR 0.47) [28]. However, a 5% risk of grade 5 toxicity was found in the ablative arm. NRG-BR002 is a phase II/III trial of SOC therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer. This trial is currently accruing patients and is expected to be completed in 2027. SABR is another critical tool along with novel small-molecule inhibitors and traditional cytotoxic systemic therapies in the management of oligometastatic breast cancer.

Conclusions

Clinical trials from the past 5 years have changed how radiation oncologists treat all stages of breast cancer. Accelerated partial breast irradiation and prone positioning allow women to complete adjuvant radiation therapy in a shorter period of time with excellent local control and cosmesis while not sacrificing DMFS or OS. RNI achieves a consistent 3–4% reduction in distant metastasis and improvement in DFS in post-mastectomy and lumpectomy patients, clearly reducing systemic risk. SABR-COMET showed that the addition of ablative stereotactic body radiation therapy to a limited number of lesions in the oligometastatic setting prolongs OS and progression-free survival. When used in conjunction with the new lines of immunotherapy, small-molecule inhibitors, and cytotoxic systemic agents, radiation therapy continues to evolve in the management of breast cancer patients. Over the next 10 years, large clinical trials like MA.39, Alliance A11202, and NRG-BR002 will finish accrual and publish their first results. These and other trials will continue to improve the treatment of women with breast cancer with radiation therapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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