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Perspective

Advances in Breast Cancer Radiotherapy and the Impact on Quality of Life

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ABBREVIATIONS

BCT: Breast Conserving Therapy; BCS: Breast Conserving Surgery; WBI: Whole Breast Irradiation; APBI: Accelerated Partial Breast Irradiation; START: Standardization of Breast Radiotherapy; ASBS: The American Society of Breast Surgeons; 3D-CRT: 3-Dimensional Conformal Radiotherapy; IMRT: Intensity Modulated Radiation Therapy; RTOG: Radiation Therapy Oncology Group; RAPID: Randomized Trial Of Accelerated Partial Breast Irradiation; SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; DCIS: Ductal Carcinoma In Situ; ECOG: Eastern Cooperative Oncology Group

Breast cancer represents the most common non-cutaneous cancer amongst women in the United States with over 300,000 cases diagnosed each year [1]. Breast Conserving Therapy (BCT) represents a breakthrough in the management of breast cancer allowing women to preserve their breast without compromising their cancer outcomes based on long term follow up from several randomized Phase III trials [2,3]. Further, studies have confirmed that women undergoing BCT have improved quality of life as compared to those undergoing mastectomy [4]. While the option of BCT has significantly improved the quality of life in women with breast cancer over the past several decades, recent advances in breast cancer radiotherapy offer the potential to further improve quality of life through reductions in radiotherapy duration, reductions in radiotherapy associated toxicities, the elimination of lymph node dissections, and the elimination of radiation therapy in subsets of women following Breast Conserving Surgery (BCS).

One significant challenge with adjuvant breast cancer radiotherapy is the duration of treatment. A standard course of radiotherapy requires 5-6 ½ weeks of daily treatment delivered to the whole breast followed by a tumor bed boost based on the techniques utilized in the randomized trials comparing mastectomy with BCT and subsequent randomized boost trials [2,3,5]. This length of treatment is one of the key reasons that up to 50% of women in some regions of the country do not receive adjuvant radiotherapy following BCS [6,7]. One potential solution to improve the compliance with adjuvant radiation therapy following BCS is to shorten the course of radiotherapy. This can be achieved with either hypofractionated Whole Breast Irradiation (WBI) or Accelerated Partial Breast Irradiation (APBI). Hypofractionated whole breast irradiation delivers larger doses of radiation per day reducing treatment duration to 3 weeks or less, with randomized trials confirming low rates of local recurrence with hypofractionated WBI and no difference compared with standard fractionation WBI [8-11]. Whelan et al. reported 10 year outcomes from the Ontario Oncology Group trial; 1,234 women with early stage breast cancer were randomized to either hypofractionated WBI (42.5 Gy in 16 fractions) or standard WBI (50 Gy in 25 fractions) with no difference in rates of local recurrence noted (6.2% v. 6.7%) [8]. Similarly data from the United Kingdom Standardization of Breast Radiotherapy (START) A and B trials confirmed no difference in outcomes with hypofractionated WBI; START A was a three arm trial randomizing women to 50 Gy in 25 fractions, 41.6 Gy in 13 fractions, or 39 Gy in 13 fractions all delivered over 5 weeks. With 9 year follow up, no difference in local control was noted [9]. START B was a two arm trial and randomized women to either 50 Gy in 25 fractions or 40 Gy in 15 fractions delivered in 5 and 3 weeks. Similarly, no difference in outcomes was noted at 10 years [9]. One concern with hypofractionation has been the potential for increased toxicity and worse cosmesis; however, rates of cosmesis and long term complications following radiotherapy were equivalent or reduced with hypofractionated WBI, alleviating concerns with hypofractionated WBI schedules [8-11]. On the contrary, START A found that the 39 Gy arm was associated with reduced toxicities following treatment and START B found the 40 Gy arm to be associated with improved breast appearance and body image [9].

An alternative to WBI that reduces treatment is APBI, which allows for the completion of adjuvant radiation therapy in one week or less [12]. APBI is different from WBI in that it treats the

area surrounding the lumpectomy cavity with a margin rather than the whole breast [12]. APBI can be delivered utilizing interstitial catheters, applicators, or external beam radiation therapy. Randomized trials comparing APBI with WBI are currently underway or recently closed; however, long term data from a randomized trial in Hungary and several studies with long term follow up have demonstrated equivalent local control with APBI and the potential for improved cosmesis and toxicity profiles [13,14]. Polgar recently presented an update of the Hungarian randomized trial that compared WBI with APBI delivered with interstitial brachytherapy or electrons. At 10 years, no difference in clinical outcomes was noted with improved cosmesis noted in the brachytherapy cohort [13]. Similarly a matched pair analysis from William Beaumont Hospital demonstrated no difference in local control between interstitial APBI and WBI at 12 years. While these studies utilized interstitial catheters, more recent techniques including applicators and external beam have been evaluated prospectively with low rates of local recurrence noted. The American Society of Breast Surgeons (ASBS) MammoSite Registry confirmed the low rates of local recurrence and toxicity in a prospective trial of over 1,400 patients, with final analysis demonstrating a local recurrence rate of less than 5% with few late complications at 5 years [15]. Increasingly, patients are opting for use of APBI as their adjuvant radiotherapy modality and as such guidelines for off protocol utilization have been created [16,17]. Moving forward, APBI may further improve quality of life by reducing treatment duration from one week to 2 days or less; however, further study is required at this time [18].

Beyond reducing treatment duration, another method to improve quality of life is to reduce the rates of acute and chronic side effects associated with breast radiotherapy. The randomized trials comparing mastectomy with BCT utilized 2-dimensional WBI. However, over the last few decades, 2-dimensional planning has been replaced by 3-dimensional conformal radiotherapy (3D-CRT). More recently, Intensity Modulated Radiation Therapy (IMRT) has emerged as a radiation therapy technique that allows for the reduction of acute and chronic toxicities in patients undergoing adjuvant breast radiotherapy [19]. Two randomized trials compared IMRT with 2-dimensional radiotherapy and found that IMRT reduced acute and chronic toxicities [20,21]. Pignol found that IMRT led to improved dose distributions and more importantly reductions in the rate of moist desquamation (31% v. 48%) in a randomized study of 330 women [20]. Donovan et al concluded that IMRT reduced rates of palpable in duration and breast appearance change based on a randomized study of 240 patients [21]. The criticism of these trials is the use of 2-dimensional therapy in the control arms, a technique which no longer represents the standard of care. However, non-randomized data has confirmed a reduction in acute and chronic toxicities with the utilization of IMRT as compared to 3-dimensional conformal radiotherapy [22-25]. A matched analysis from Fox Chase confirmed a reduction in the rates of desquamation compared with conventional therapy. Because of the cost associated with IMRT, recent studies have attempted to identify subsets of women who benefit the most from the utilization of this technique. These studies have confirmed that while the largest benefit to IMRT is with larger breast women, that all patients benefit from the utilization of IMRT to deliver either standard or hypofractionated WBI [22]. While most data with IMRT is based on WBI there has been study of IMRT with the delivery of APBI. Concerns have been raised regarding potential increased toxicities associated with 3D-CRT APBI based on prospective data from RTOG 0319 and the RAPID trial [26,27]. IMRT offers the potential to reduce these side-effects with studies evaluating the role of IMRT in external beam APBI demonstrating low rates of toxicity [28].

The introduction of the Sentinel Lymph Node Biopsy (SLNB) altered the surgical paradigm for management of the axilla in breast cancer and has led to a reduction in the incidence of lymphedema [29]. However, patients still underwent a completion Axillary Lymph Node Dissection (ALND) when positive nodes were identified at the SLN. Recent data from the American College of Surgeons Oncology Group Z011 trial has changed this; the trial was a phase 3 non-inferiority that randomized women with clinically node negative invasive breast cancer found to have 1-2 positive SLN's to completion ALND or no further axillary treatment as part of breast conserving surgery. All patients underwent post-operative whole breast irradiation with no regional nodal irradiation given. Though the trial failed to complete accrual, no difference in rates of overall survival, disease free survival, local recurrence, or regional recurrence was noted at 5 years [30,31]. These findings have the ability to improve the quality of life for women with limited SLN positivity as sparing them an ALND would likely reduce the rates of lymphedema and shoulder dysfunction while not subjecting them to regional nodal irradiation.

Finally, one potential area of improvement in quality of life is identifying those patients that do not require adjuvant radiation therapy. In both invasive and non-invasive breast cancers, randomized and prospective studies have consistently demonstrated a local recurrence benefit with the addition of radiation therapy following breast conserving surgery which has been confirmed by meta-analyses [32-35]. It should be noted that these studies utilized clinical (ex. age) and pathologic (ex. grade, size) to risk stratify patients [36]. However, each study has confirmed that there exists no truly low risk group where adjuvant radiation therapy fails to provide a local control benefit. Moving forward, the potential exists for the utilization of tumor genetics to better risk stratify patients who are truly low-risk and therefore do not require adjuvant radiation therapy. Such technology is already in place and has been utilized to risk stratify and quantify the benefit of systemic therapy in patients with invasive breast cancer; importantly, these assays have been validated utilizing prospective data from cooperative group trials [37-39]. However, at this time, there exists limited data on the utilization of such assays for risk stratification with respect to delivery of radiotherapy. For example, Solin utilized a multigene expression assay to examine patients with DCIS treated on the ECOG E5194 trial; however, even the "low-risk" score group had an 11% risk of local recurrence at 10 years [40]. Moving forward, these types of assays must be further refined in the search for a truly low-risk group of patients not requiring adjuvant radiation therapy [41]. Identifying a truly low-risk cohort would eliminate radiation therapy for such patients and improve quality of life.

Advances in radiation therapy offer the potential for

significant improvements in the quality of life of breast cancer patients. Whether it is through innovative treatment techniques and delivery strategies or identifying subsets of patients who can be spared toxicity causing therapy, the potential exists for further improvements in the quality of life of breast cancer patients moving forward.

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