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RADIATION ONCOLOGY (W WOODWARD, SECTION EDITOR)

New Frontiers in Hypofractionation for Regional Nodal Irradiation in Breast Cancer

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Abstract

Purpose of Review In recent years, there have been a number of small, yet notable practice changes in the delivery of postmastectomy radiation therapy (PMRT) in breast cancer patients. Herein, we describe the role of PMRT and its evolving delivery with hypofractionated regimens.

Recent Findings The UK START trials and whole-breast hypofractionation studies established the safety and effectiveness of accelerated radiotherapy. This has inspired further investigations of similar principles in patients with reconstruction, acute and late toxicities associated with hypofractionated regimens, socioeconomic benefit, and evolving delivery techniques.

Summary Overall, results from clinical trials evaluating hypofractionation for RNI or PMRT appear promising despite the limited length of follow-up. Ongoing clinical trials will provide valuable data on the safety of hypofractionation in breast cancer patients with immediate reconstruction. Hypofractionation for PMRT represents high-quality care that is not only more convenient for patients but also more cost-effective for the healthcare system.

Keywords Breast cancer · Post mastectomy radiation therapy · Hypofractionation · Regional nodal irradiation · Chest wall reconstruction

Introduction

In the United States, the estimated number of new diagnoses and deaths from breast cancer in 2020 is approximately 279,100 and 42,690, respectively [1]. Regional lymph node involvement is an important prognostic factor, associated with increased risk of recurrence and lower overall survival rates compared to node-negative patients [1–3]. The standard treatment of breast cancer involves a multidisciplinary approach including surgery, radiotherapy, and systemic treatment. Diagnostic imaging, pathology findings, and postoperative outcomes guide adjuvant radiotherapy management and systemic treatment options. The National Comprehensive Cancer Network (NCCN) guidelines recommend postmastectomy radiation therapy (PMRT) based on tumor characteristics including size greater than 5 cm, positive margins, and 4 or more positive axillary lymph nodes [4].

In recent years, there have been a number of small, yet notable practice changes in the delivery of PMRT. Perhaps the most controversial is the strong consideration of PMRT in women with 1 to 3 positive axillary lymph nodes [4]. This recommendation is subject to debate given conflicting reports on therapeutic benefit [4–9]. However, in the midst of this ongoing debate, there has been a steady but significant increase in the receipt of PMRT for 1–3 positive nodes, from 19.1 in 2003 to 30.3% in 2012 [10]. Another noticeable change in the practice pattern is the growing interest in delivering PMRT with hypofractionated regimens of higher doses per radiation. In the United States, utilization of hypofractionated PMRT is uncommon but has increased from 0.8 to 1.7% of patients receiving PMRT between 2004 and 2014, with the largest increase at academic facilities [11]. Increased interest in hypofractionated PMRT regimens is attributable to the recent publication of randomized trials demonstrating its safety and efficacy. Herein, we describe the role of PMRT and its evolving application with hypofractionated regimens.

This article is part of the Topical Collection on *Radiation Oncology*

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Impact of PMRT on Locoregional Outcomes

The indications for postmastectomy radiation therapy (PMRT) have evolved and yet remain controversial. It is a widely acceptable standard-of-care for patients with multifocal tumors, locally advanced disease, or at least four positive node-negative patients [9]. Otherwise, most clinicians risk stratify based on factors predictive of locoregional failure. These include high T stage, presence of lymphovascular invasion, high grade, young age or premenopausal patients, close or positive margins, triple negative status, and no recommendation for systemic therapy. Current NCCN guidelines recommend conventional fractionation with 1.8–2.0 Gy per fraction daily over 5–6 weeks for management of patients who meet the criteria for PMRT, in addition to irradiation of suspicious regional nodes [4].

The first large-scale randomized control trials known as the Danish Breast Cancer Cooperative Group studies and British Columbia trials demonstrated the association of overall survival benefit with PMRT in patients also requiring axillary lymph node dissection [6, 8, 12]. In addition, these landmark trials demonstrated an association of PMRT with increased disease-free survival and decreased locoregional failure. Prior to these studies, the first meta-analysis of over 3400 patients in six historical breast cancer trials suggested an association of survival decrement of 1–10% with PMRT [13]. However, this meta-analysis included older studies that were limited by poor patient selection, outdated systemic treatments, and radiotherapy technique, such that the deaths were later attributed to late cardiac deaths upon re-analysis which demonstrated PMRT's association with improved breast cancer-specific survival [14].

Following the established benefit of PMRT including locoregional control, the reduction of normal tissue injury including late cardiac and pulmonary toxicity posed a challenge particularly for patients with internal mammary node involvement, central or medial tumors, or immediate chest wall reconstruction. Thus, the conventional fractionation regimen of 50 Gy in 25 fractions with an optional scar boost became widely adopted for PMRT. However, the subsequent adoption of whole-breast hypofractionation following breast conserving surgery have inspired hypothesis on its role as a postmastectomy radiotherapy regimen.

Extrapolation from Historical Clinical Trials

Hypofractionation delivers higher doses of radiation in fewer visits, which tends to lower the effects of accelerated tumor growth that typically occurs during the later stages of radiotherapy. Based on principles of radiobiology, the inherent benefit of hypofractionation is the accelerated killing of cancer cells at higher doses per fraction. With modest increases in doses per fraction, it is believed that late normal tissue damage such as fibrosis can be controlled. The earliest use of a hypofractionation regimen in the management of regional nodes were in the UK START trials.

The START A and B trials excluded patients with immediate reconstruction following mastectomy but compared hypofractionation regimens to the standard fractionation of 50 Gy in 25 fractions over 5 weeks [15, 16]. In START A, the hypofractionated group received 41.6 Gy in 13 fractions or 39 Gy in 13 fractions, and 15% (336) of study participants received PMRT while 14% (318) received regional nodal irradiation (RNI). Compared to the START B trial which compared 40 Gy in 15 fractions over 3 weeks to conventional fractionation, 8% of the study cohort received PMRT while 7% had regional nodal irradiation. Compared to standard fractionation, these trials reported lower rates of breast edema, shrinkage, and telangiectasias in the hypofractionation group as well as lower rates of brachial plexopathy in the RNI with hypofractionation group, suggesting improved breast cosmesis without compromise on local control outcomes [17]. Later, studies built upon this findings and reported statistically significant increase in breast cancer-specific survival in patients randomized to receive 37.5 Gy in 16 fractions compared to those who received no further therapy [8]. Additionally, Whelan and colleagues demonstrated that hypofractionated whole-breast irradiation using 42.5 Gy in 16 fractions over 22 days is non-inferior to conventional fractionation of 50 Gy in 25 fractions [18]. Findings from the UK START trials and subsequent whole-breast hypofractionation studies established the safety and effectiveness of accelerated radiotherapy and set the stage for further exploration in postmastectomy with regional nodal irradiation setting.

Clinical Trials and Retrospective Studies of Hypofractionated Regional Nodal Irradiation

Historical breast cancer trials involving adjuvant radiotherapy demonstrated improved survival using conventional fractionation of 1.8–2.5 Gy per fraction over 5 to 7 weeks of treatment. Presently, data on hypofractionation of postmastectomy with regional nodal irradiation is limited to few randomized control trails and institutional studies. A recently published phase III trial conducted in the Chinese Academy of Medical Sciences suggests non-inferiority between conventional fractionated (50 Gy in 25 fractions) and hypofractionated regimen (43.5 Gy in 15 fractions) in a postmastectomy setting. In this study, 820 patients enrolled between 2008 and 2016; the five-year cumulative incidence of locoregional recurrence in the chest wall or regional nodes reported was 8.3% in the conventional treatment group compared to 8.1% in the hypofractionated group [19••]. Unlike the

study participants of the TomoBreast study, this open label study led by Wang and colleagues enrolled high-risk patients with stage T3–4 disease or at least four pathological positive axillary lymph nodes [19••]. However, this trial excluded patients with gross non-axillary nodes such as supraclavicular or internal mammary nodes. A limitation was that reconstruction were excluded from the study, making it difficult to extrapolate these findings to breast cancer patients receiving mastectomy in the U.S.A., where up to one-third of patients receive immediate reconstruction [20]. Also, in addition to the chest wall, the nodal volumes treated were limited to level III axillary nodes and supraclavicular region. Radiation was delivered with two-dimensional techniques. Despite these limitations, this study was the first randomized controlled trial demonstrated the non-inferiority of hypofractionated radiotherapy to conventional fractionated radiotherapy and suggests a safe utilization in postmastectomy without reconstruction for patients with high-risk breast cancer requiring nodal irradiation [19••].

The tolerance and efficacy of a highly accelerated regimen of hypofractionation has been tested in a prospective study of postmastectomy radiation with or without amofostine, a cytoprotective adjuvant. Koukourakis and colleagues enrolled 112 patients from 2003 to 2010 in Greece, all of whom met the criteria for postmastectomy radiation at the time based on high T stage (T3/T4) and/or presence of four or more positive nodes following simple or modified radical mastectomy without reconstruction [21]. All patients received 10 consecutive fractions of 3.5 Gy for a total of 35 Gy to the chest wall and axilla and supraclavicular nodes followed by a total boost of 8 Gy in 2 fractions to the chest wall scar using electrons. An additional 3.5 Gy was administered to the axilla and supraclavicular in the presence of extensive nodal disease. Despite the limitations of a small control group accounting for 18.7% of participants who declined amofostine, this study demonstrated tolerance of a three-week hypofractionated regimen and improved efficacy based on their 97% projected 5-year local relapse-free survival. However, the effects of this regimen in reconstructed patients and necessity of amofostine are unknown.

More recently, a prospective, single-arm phase II trial (NCT01417286) investigated a novel hypofractionation schedule for PMRT in 67 women with stage IIA to IIIC invasive breast cancer [22•]. The study included patients with locally advanced breast cancer, high-risk features (T4 disease, lymphovascular invasion, close margins, young age, hormone–receptor negativity, or an extensive intraductal component); had received neoadjuvant chemotherapy; or had reconstructed chest walls, implants, or temporary expanders. The investigational PMRT regimen consisted of 36.63 Gy in 11 fractions over 11 days to the chest wall and the draining regional lymph nodes, followed by an optional mastectomy scar boost of four fractions of 3.33 Gy. After a median follow-up of 32 months, the study met the primary end point of no grade 3 or higher toxicities. Of the 41 patients (61%) who had chest wall reconstructions, three had expanders were removed for infection before RT, 24% (9 of 38) experienced implant loss or failure, and 8% (3 of 38) required unplanned surgical correction rate, thus resulting in an overall complication rate of 32% which is comparable to previously published rates [23, 24]. While this regimen appears to be safe and effective, questions surrounding the safety and efficacy of hypofractionation for breast reconstruction and regional nodal volume persist.

A large institution-based study in Thailand led by Pinitpatcharalet and colleagues reported similar outcomes between patients treated with conventional fractionation (25 fractions of 1.8–2.0 Gy) and hypofractionated regimen (16–18 fractions of 2.65 Gy) between 2004 and 2006. The authors reported similar five-year locoregional control and disease-free survival between the two arms. This was the first report to suggest statistically significant increase in 5-year overall survival following hypofractionation in the postmastectomy setting (73%) in comparison to the conventional fractionated arm (62.7%) [25]. Likewise, Rastogi and colleagues have reported favorable experience of patients' tolerability and minimal toxicity from their prospective trial conducted from 2014 to 2016. Their study compared conventional fractionation of 50 Gy in 25 fractions to modest hypofractionation regimen of 42.72 Gy in 16 fractions [26•]. This postmastectomy trial of 100 relatively healthy women randomized into both groups included an even distribution of patients who received supraclavicular nodal irradiation and neoadjuvant chemotherapy. The authors reported similar local and regional recurrence and overall survival in both groups. While the difference was not statistically significant, the five hypofractionated PMRT patients with locoregional recurrence had triple negative, high-grade, or increased number of positive nodes [26•].

The earliest randomized phase III trial, TomoBreast, compared conventional radiation to hypofractionated tomotherapy (NCT00459628) with simultaneous integrated boost. The study enrolled 121 women in Brussels from 2007 to 2011, with stage T1–3N0M0 or T1–2N1M0, breast cancer. The primary endpoint was pulmonary or cardiac toxicity while locoregional recurrence was the secondary endpoint [27]. The control group included postlumpectomy and mastectomy patients randomized to receive 50 Gy in 25 fractions over 5 weeks to the breast/chest wall, supraclavicular-axillary field if node positive, and sequential boost of 16 Gy/8fractions. The hypofractionation group received 42 Gy in 15 fractions to the breast/chest wall and nodes if positive, and an integrated boost of 9 Gy in 15 fractions to the lumpectomy cavity, for a total dose of 51 Gy in 15 fractions over 3 weeks. In this study of the 69 evaluable trial patients, 28 had undergone a mastectomy, of which 17 were in the hypofractionated experimental arm [16].

Much anticipated are the results of novel trials investigating the efficacy and toxicities of "ultra" hypofractionated RT

for RNI, such as the FAST Forward RNI trial. The results of FAST Forward trial investigating 40 Gy in 15 fractions versus 26 Gy or 27 Gy in 5 fractions over one week in patients receiving whole-breast RT was recently published. At a median follow-up of 5.9 years, 5-year IBTR was 2.1% for 40 Gy, 1.7% for 27 Gy, and 1.4% for 26 Gy. The difference between groups did not exceed a pre-defined upper limit of 1.6%, and thus, both one-week regimens were non-inferior (40 Gy vs. 27 Gy: HR 0.86, 95% CI 0.51–1.44; 40 Gy vs. 26 Gy: HR 0.67, 95% CI 0.38–1.16) [28]. Following on its heels, the FAST Forward nodal study opened in 2015 with normal tissue endpoints. In 2018, this was modified to a two-arm study comparing 40 Gy in 15 fractions over three weeks versus 26 Gy in 5 fractions over one week in breast cancer patients treated to the regional lymph nodes [29]. Two-year follow-up will be completed and reported by early 2021.

Toxicity Considerations

One of the concerns of adopting hypofractionation regimen in the postmastectomy setting is the fear of acute and late toxicities which could translate into poorer long-term quality of life for patients. In the 1960s and 1970s, trials of early attempted at hypofractionated PMRT resulted in unacceptable rates of brachial plexopathy, shoulder dysfunction, lung fibrosis, arm edema, and in some cases, paralysis [30]. The caveat is that these older trials increased the daily dose of RT without modifying the total dose. Furthermore, the techniques used to deliver RT were not 3D-based conformal techniques currently available in practice, which resulted in extremely high radiobiological doses to normal tissues, particularly in the region of the brachial plexus. Although our understanding of radiobiological concepts and techniques are considerably more advanced now, these issues explain concerns about hypofractionation when treating the supraclavicular region. In the postmastectomy setting, an additional issue that needs to be resolved is whether hypofractionation exacerbates breast reconstruction complications beyond the complications observed with standard fractionation in the PMRT setting [23].

Chest Wall and Skin Toxicity

In the hypofractionated TomoBreast group, at 2 years after treatment, skin toxicity of grade 1 or higher was noted in 30% of the patients compared to 60% in the control arm [27]. Of note, 49% of patients in the study received adjuvant chemotherapy while radiation was administered concurrently in majority (76%) of these chemotherapy recipients, which could have intensified chest wall/skin reaction reported. Interestingly, the proportion of patients receiving concomitant chemotherapy was higher among the experimental arm (39%) compared to the control arm (30%). Similarly, subcutaneous toxicity also known as breast/chest wall fibrosis was higher in the control arm both at the 1st and 2nd year study time points compared to the hypofractionated tomotherapy group.

Likewise, Wang and colleagues reported less frequent grade 3 acute skin toxicities in the hypofractionated group (3% of cohort) compared to 8% of the conventional fractionated group, while the frequency of grade 1–2 skin toxicity was comparable in both groups [19••]. In addition, Koukourakis and colleagues reported no confluent moist desquamation (grade 3) or skin necrosis (grade 4) among their study cohort which included patients that declined amofostine in the setting of accelerated and hypofractionated postmastectomy radiation [21]. Similarly, no grade 3 erythema, radiation dermatitis, chest wall pain, and subcutaneous edema was reported during the 16-day period of treatment, defined as acute toxicity phase. However, at a median follow-up of 44 months, assessment of late radiation toxicity to the chest wall revealed that 18.7% of all patients had intense (grade 2) skin telangiectasias, 7.1% had definite firmness in the boost site, 1.8% had moderate chest wall pain, and 4.4% had moderate/tolerable subcutaneous edema.

Cardiac Toxicity

Wang and colleagues reported a lower mean heart dose of 0.3 Gy in the hypofractionated group compared to 0.8 Gy in the conventional group [19••]. Furthermore, in their study, only 55% of patients with HER2-positive disease (60/111) in the conventional treatment group and 56% (76/135) in the hypofractionated treatment group received trastuzumab. This limits the ability to quantify cardiac risks with hypofractionation when anti-HER2 therapy is concurrently delivered [31]. The TomoBreast study reported no significant change in cardiac function between its control and hypofractionated arm at 2 years [27]. These results are reassuring, as 14% (10 of 69) patients received trastuzumab, 8 of whom were randomized to the hypofractionated regimen. Specifically, there was no significant difference in observed changes in the left ventricular ejection fraction of 4.8% of patients in the conventional fractionation compared to 4.6% in the tomotherapy hypofractionated arm.

Findings described by Rastogi and colleagues suggest an risk of increased mean heart dose with hypofractionated regimen, irrespective of chest wall laterality [26•]. Specifically, they reported a mean heart dose of 6.25 Gy and 1.12 Gy in the hypofractionation group compared to 4.86 Gy and 0.57 Gy in the conventional fractionation arm in patients with left- and right-sided breast cancer, respectively. The risks of cardiac toxicity are increased with internal mammary nodal (IMN) irradiation, thus raising a concern with hypofractionated PMRT requiring such coverage. However, Poppe and colleagues reported that 28% of their study cohort required IMN coverage and yet the reported mean heart

dose was 1.3 Gy (0.26–3.81) and a V20 of 0.3% based on retrospective evaluation of randomly selected dose–volume histogram analysis [32].

Pulmonary Toxicity

At 2 years, the TomoBreast study reported statistically significant changes in the diffusion capacity of lungs (DL_{co}) in 29% of patients in the control arm compared to 7% of patients in the hypofractionation arm, suggesting decreased lung toxicity of grade 1 or higher as a result of shortened treatment [27].Also, a greater decline of grade 1 or higher FEV_1 in control arm (21%) was noted compared to patients in the hypofractionation arm (15%). Likewise, symptomatic radiation pneumonitis was not reported by Wang and colleagues, while the difference in frequency of grade 1–2 pneumonitis was not statistically significant [19••]. A similar finding of decreased rate of grade 2 or higher radiation-induced pneumonitis was reported by Rastogi and colleagues [26•]. In their prospective trial of 100 patients, 2% of patients in the hypofractionation group reported grade 2 pneumonitis, compared to 6% of patients in the conventional fractionation arm.

Despite these promising findings of decreased rate of pneumonitis with hypofractionation, the V20 for ipsilateral lung of patients receiving shorter radiotherapy regimen should be closely monitored as suggested by Rastogi and colleagues. Specifically, the V20 for ipsilateral lung was 24.25% in their hypofractionation study group compared to 20.85% in their conventional group [26•]. Koukourakis and colleagues tested the hypothesis of amofistine's protective properties against fibrosis in the setting of an accelerated hypofractionated regimen and reported no case of pneumonitis in the acute phase for all patients including those who did not receive amofostine [21]. However, they reported that 21.4% of patients had barely evident CT changes of pneumonitis, considered grade 1, and 3.6% of patients had evidence of CT changes considered grade 2 pneumonitis at a median follow-up of 44 months. This finding highlights the importance of long-term assessment of late pulmonary toxicity in patients receiving hypofractionated PMRT.

Brachial Plexopathy and Lymphedema

The risk factors for lymphedema include surgical management of the axilla and radiation [33–37], and it remains a complication with a significant impact on quality of life and well-being [38, 39]. A primary concern regarding higher doses per fraction for nodal irradiation is the elevated risk of lymphedema as a long-term toxicity. Wang and colleagues reported no brachial plexopathy or rib fracture in their study. This finding was attributed to the low EQD2 of 51 Gy for the brachial nerve in comparison to the established dose tolerance of the brachial plexus (66 Gy) [19••]. The incidence of grade 1 lymphedema reported was 5% in both the conventional and hypofractionation groups. There was one grade 2 lymphedema in the hypofractionated group compared to none in the control group [19••]. Likewise, Koukourakis and colleagues reported minimal pain from brachial plexopathy and circumferential arm lymphedema of 4–6 cm (grade 2) in 1.8% of their participants at a median follow-up of 44 months [21]. Of note, their study reported the incidence of grade 1 and 2 shoulder dysfunction, which was not significantly different between both groups. Finally, Rastogi and colleagues reported a finding of grade 2 or higher lymphedema in 12% of their hypofractionation cohort compared to 10% that received conventional fractionation, which was higher than incidences reported in other studies [26•]. Thus, while lymphedema remains a risk in patients receiving hypofractionated PMRT and regional nodal irradiation, the overall rates are quite low and can be mitigated with early intervention.

Ongoing Clinical Trials of Hypofractionation in Breast Cancer Patients with Reconstruction

The fear of reconstruction complications including skin necrosis, infection, implant rupture, capsular contracture, and overall implant failure has limited the rapid adoption of hypofractionation in the postmastectomy radiation setting. However, there is limited data to be extrapolated from the recent publication of the five-year update from the multi-institutional prospective phase II study of hypofractionation PMRT using 36.63 Gy in 11 fractions with an optional scar boost of 13.32 Gy in 4 fractions, which included 43 patients (62%) with reconstruction [22•]. In this cohort, majority (93%) had immediate reconstruction which included temporary expanders (88%), immediate implants (7%), and prior augmentation implants (5%). In the reconstruction PMRT group, 35% of patients had grade 3 or 4 radiation-induced reconstruction complications [22•]. In their interim analysis at a median follow-up of 32 months, the reported complication rate was 32%, including the rate of implant loss of failure at 24% (9 out of 38) and unplanned surgical correction rate of 8% (3 of 38). This is similar to a phase II trial of conventional PMRT using double-scatter proton radiation in which 33% of patients had unplanned surgical re-intervention rate to their reconstructed breast at 5 years [40]. While we await the details of the reconstruction complication and management required at the 5-year follow-up from Poppe and colleagues, their study revealed that the hypofractionation regimen was well tolerated as 28% of patients with grade 2 dermatitis recovered within six months. Other late grade 2 toxicities reported in this study was chest wall pain in 8% of patients, fatigue in 3%, and one patient with late grade 2 lymphedema which was attributed to extensive axillary dissection [32•].

The importance of investigating the effect of hypofractionation on reconstruction outcomes is evidenced by two ongoing clinical trials investigating hypofractionation for reconstructed breast, chest wall, and regional nodes. The FABREC trial (NCT03422003) is a multi-center, randomized clinical comparing hypofractionated PMRT (42.56 Gy in 16 fractions to the chest wall and 39.9 Gy to the lymph nodes) with standard fractionated PMRT (50 Gy to the chest wall and 46–50 Gy to the lymph nodes) in women who underwent mastectomy followed by immediate reconstruction. The primary outcome is the change from baseline patient-reported outcomes at six months. Similarly, the RT CHARM (NCT03414970) is a randomized phase 3 trial comparing conventional PMRT (50 Gy in 25 fractions over 5–6 weeks) to hypofractionated PMRT (42.56 Gy in 16 fractions over 3–4 weeks) to both chest wall and/or reconstructed breast and regional nodes in patients with stage IIA-IIIA. The primary outcome is the rate of breast reconstruction complication at 24 months. These ongoing trials will provide the level I evidence and confidence for radiation oncologists in the United States to adopt this feasible, safe. and effective regimen.

Socioeconomic Benefit and Quality of Life

Beyond the established safety and uncompromised local control benefit of hypofractionation of RT following breast conserving surgery, and few studies that have explored its feasibility in post-mastectomy radiation, there are socioeconomic benefits for shorter radiotherapy regimens. First, hypofractionation boasts of decreased treatment which translates in decreased cost of cancer care. This is worth noting as the financial toxicity of cancer treatment remains a growing public concern, and it disproportionately affects low-income, uninsured, younger, and minority patients [41]. Considering that minority patients are disproportionately diagnosed with more aggressive subtypes of breast cancer that would require postmastectomy radiation [42], efforts are needed to mitigate the additional sources of financial distress including unnecessarily prolonged radiation course that is not proven to have a significantly increased survival benefit.

Further, hypofractionation of the chest wall and regional nodes allows for increased availability of machine to treat more patients, particularly in resource-limited settings. As described by Rastogi and colleagues who led the prospective trial in India, patients who received hypofractionated regimen only had to stay for 20 days in contrast to the 35 days of stay for the those in the conventional fractionation group [26•]. This shorter treatment course increased convenience for patients, especially those with high-risk disease for whom travel distance and associated costs of prolonged care can influence their adherence to treatment. Finally, patients treated with hypofractionation to the chest wall/breast and regional nodes in the TomoBreast study reported improved role and cognitive functioning, quality of life, and fatigue after radiation [43]. In addition to the proven cosmetic advantage of hypofractionated radiotherapy in the breast-conserving setting, the benefits of a shorter radiotherapy regimen in postmastectomy patients likely outweighs the medically manageable adverse effects, even with reconstruction.

Evolving Practice Patterns in Techniques for Hypofractionated Regional Nodal Irradiation

Previously described retrospective studies and completed randomized trials have predominantly delivered hypofractionation using 3D conformal radiotherapy with tangential photon beam arrangement or with 2D treatment involving electrons. However, in the age of advanced radiotherapy techniques including intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and proton beam therapy, increased dose homogeneity can be achieved particularly when radiating regional nodes (see case studies). While these modern alternative techniques to deliver hypofractionation involving regional nodes increases treatment complexity, it is proven to reduce radiation dose to the heart and lung, particularly when covering the IMN [44, 45].

The feasibility of a multi-beam inverse planned IMRT to deliver PMRT for reconstructed patients has been reported [46,47•]. In addition, the use of VMAT to deliver PMRT can reduce treatment time and increase sparing of normal tissue particularly in combination with deep-inspiratory breath hold technique [48•]. Despite the low-dose radiation exposure secondary to VMAT which might deter its adoption as a PMRT technique, the ease of regional nodal radiation without compromising dosimetric constraints of the contralateral breast or reconstructed chest wall, heart, lung, and brachial plexus makes it a desirable hypofractionation technique. However, similar to the ongoing RADCOMP trial (NCT02603341) comparing the effectiveness of proton therapy to photon therapy in reduction of major cardiovascular events, prospective trials are needed to validate the effectiveness and benefit of alternate modalities of delivering hypofractionated regional nodal irradiation besides 3D conformal technique.

Techniques of Hypofractionation to Left-Sided Reconstructed Chest Wall with Regional Nodal Irradiation

While 3D-conformal radiation therapy (3D-CRT) is the most common technique utilized for delivering hypofractionated RNI, newer techniques such as VMAT and proton therapy are emerging as tools to help achieve treatment planning goals.

Hypofractionated RNI with proton therapy has been tested in a clinical trial conducted at the Mayo Clinic, in which 82 breast cancer patients were randomized to standard fractionation (50 Gy/25 fractions) versus hypofractionated (40 Gy RBE/15

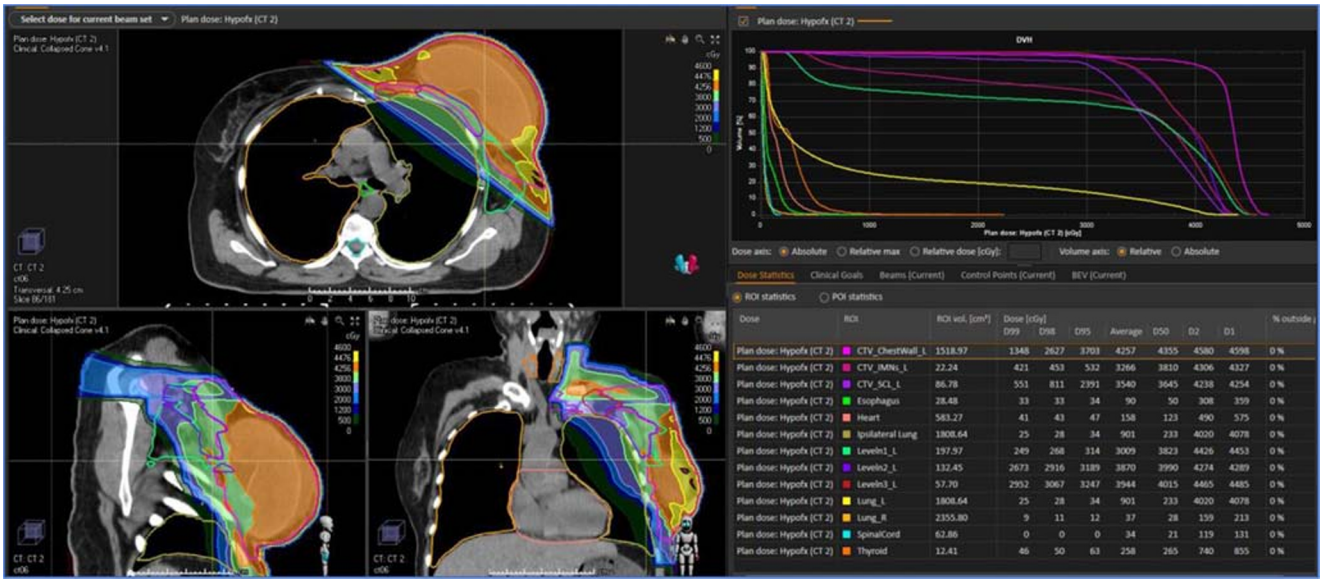

Fig. 1 3D-CRT plan of hypofractionation of a patient's reconstructed left chest wall and RNI (3990 cGy in 15fx with 266 cGy boost)

fractions) to the chest wall and regional nodes [49]. The primary endpoint was grade 3 or higher late adverse effect or unplanned surgical intervention at 24 months. Increased reconstruction complications were reported in a subset of the patients treated with hypofractionated protons [50] indicating that this approach should be studied cautiously within a trial setting and there remains much to be learned regarding the impact of linear energy transfer (LET) in hypofractionated proton therapy.

Hypofractionated RNI with VMAT was recently studied by investigators in South Korea, who performed a propensity-score-weighted comparison of radiation-related toxicity according to fractionation and modality [51••]. The analysis included 4209 patients treated with 3-dimensional conventional fractionation and 1540 patients treated with hypofractionated RT, of whom 768 received hypofractionated-3D and 772 received hypofractionated-VMAT, mostly 40 Gy/15 fractions between 2005 and 2017 at a tertiary academic center. Hypofractionated-VMAT significantly reduced grade 2+ acute and subacute toxicities compared to conventional fraction-3D (odds ratio (OR) 0·11, $p < 0·001$) and hypofractionated-3D (OR 0·45, $p = 0·010$). The 3-year cumulative rate of late toxicities was lowest in patients treated with hypofractionated-VMAT (18·0% (20·1%, 10·9%, and 13·4% in patients treated with conventional

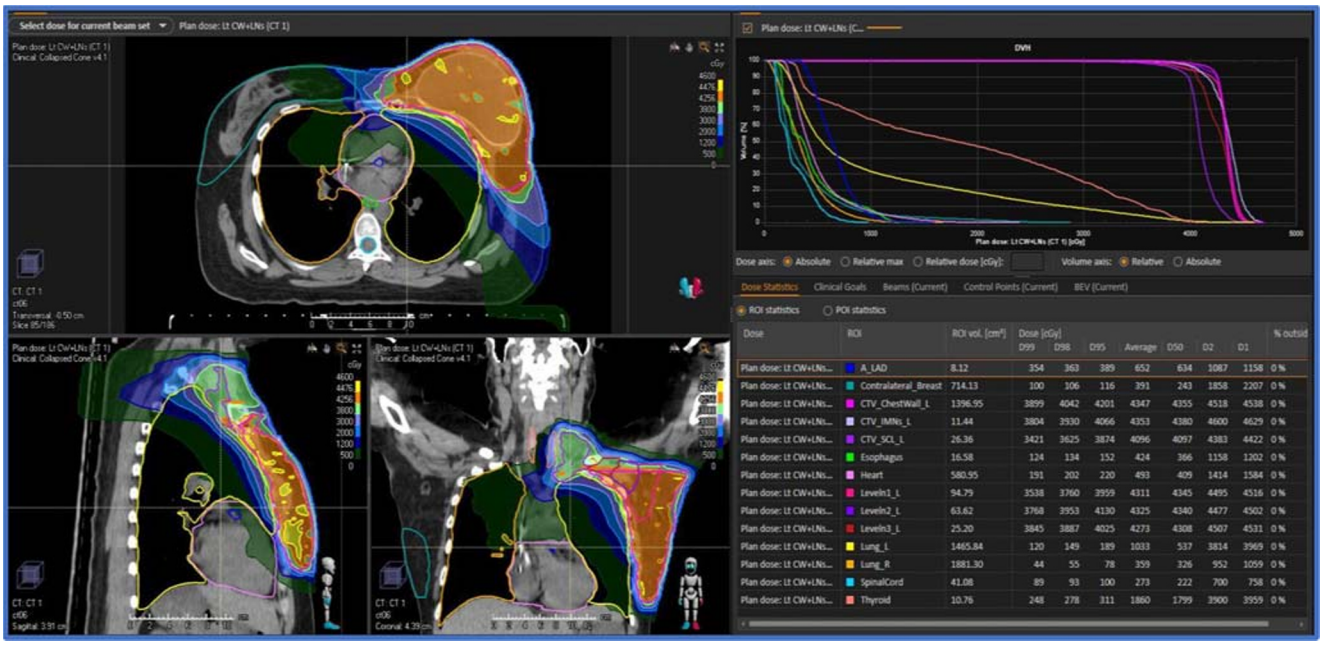

Fig. 2 VMAT plan of hypofractionation of a patient's reconstructed left chest wall and RNI (3990 cGy in 15fx with 266 cGy boost)

fraction-3D, hypofractionated-3D, and hypofractionated-VMAT, respectively; $p < 0{\cdot}001$). Hypofractionated-VMAT also resulted in fewer late toxicities than hypofractionated-3D and conventional fraction-3D, indicating hypofractionated-VMAT as an individualized approach.

The case studies below describe these 3 planning techniques (3D-CRT, VMAT, and Protons) for delivering hypofractionated RNI in breast cancer patients with left-sided disease and implant reconstruction. Diffuse inspiratory breath hold techniques were combined with the photon techniques in order to minimize doses delivered to the heart.

Case Study I: 3D Conformal Radiation Therapy (3D-CRT)

The prescription for this case was 39.9 Gy in 15 fractions to the left chest wall and regional nodes including axilla, supraclavicular, and internal mammary chain with a boost of 2.66 Gy in 1 fraction to the left chest wall and internal mammary nodes. (Fig. 1) Energies of 6 and 10 MV were used for tangent fields, in conjunction with daily 3 mm bolus. A wide tangent approach was used to capture the internal mammary nodes. The supraclavicular field used 15 MV and prescribed to 3.5 cm depth. A monoisocentric technique was used to decrease the patient time on the treatment table. To optimize homogeneity within the chest wall volume, multiple field in fields were used. Clinical hot spots in the chest wall were 108%. The ipsilateral lung V20 was 19% and V5 was 35%. The mean heart dose was 1.58 Gy. CTV_IMNs_L received 40 Gy to 32%, and CTV_CW_L received 42.56 Gy to 80% and 40 Gy to 92%.

Case Study II: Volumetric Modulated Arc Therapy (VMAT)

The prescription for this case was 39.9 Gy in 15 fractions to the left chest wall and regional nodes including axilla,

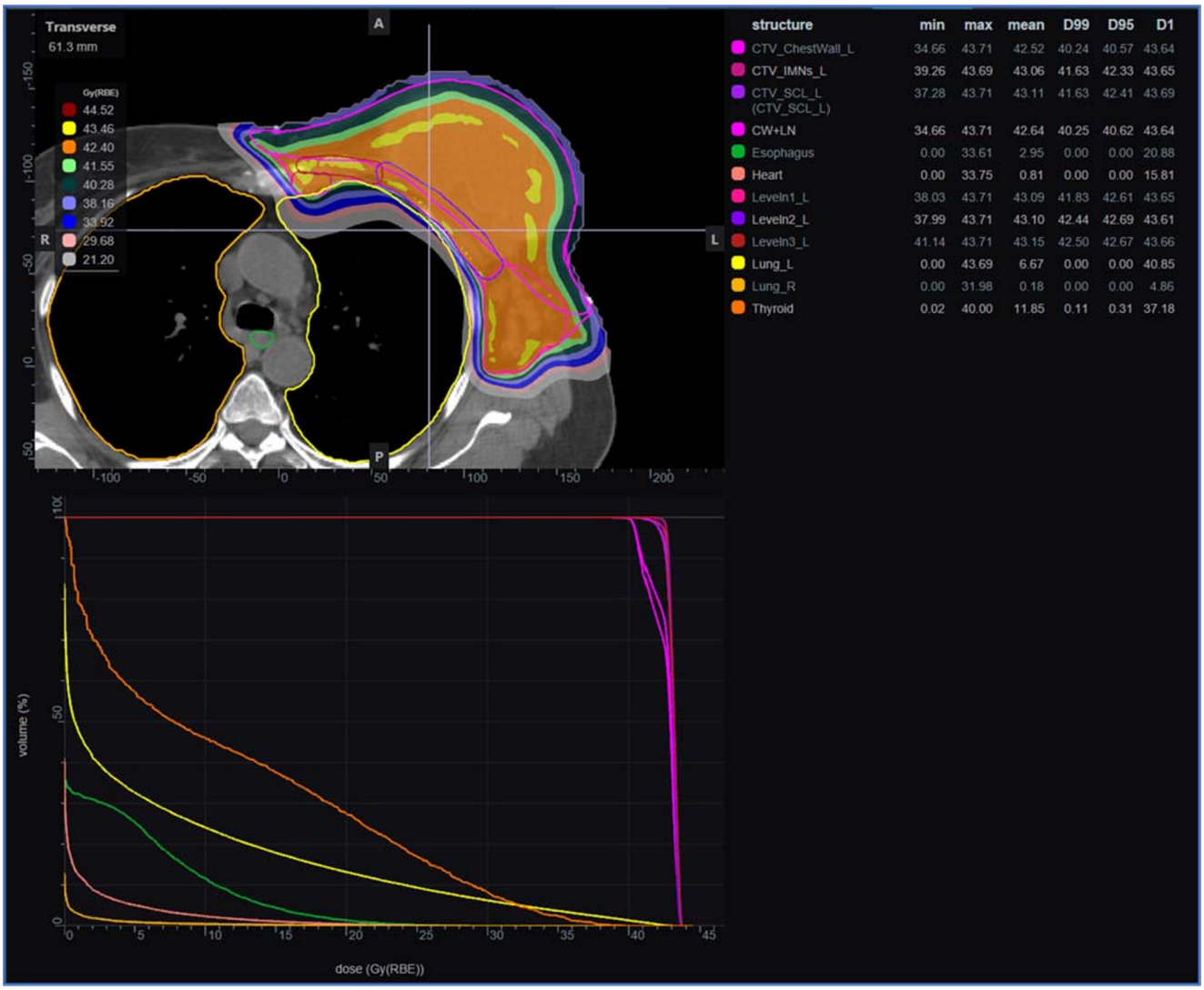

Fig. 3 PBRT plan of hypofractionation of a patient's reconstructed left chest wall and RNI (4240 cGy in 16fx)

supraclavicular, and internal mammary chains with a boost of 2.66 Gy in 1 fraction to the left chest wall and internal mammary nodes. (Fig. 2) The energy used for both courses was 6 MV, with a 3 mm daily bolus over the chest wall. The initial course of treatment used four arcs. Two arcs had jaws locked below the arm and rotated from gantry 181 to gantry 300. Two arcs treated the full extent of the treatment volume and had shorter arc ranges to avoid treating through the patient's arm. The boost course used two arcs, with the superior jaw locked below the arm. The plans were optimized using multi-criteria optimization in Raystation. The ipsilateral lung V20 was 18% and V5 was 53%. The mean heart dose was 4.93 Gy. The CTV_IMNs_L received 40 Gy to 96%, and CTV_CW_L received 42.56 Gy to 90% and 40 Gy to 98%.

Case Study III: Proton Beam Radiation Therapy (PBRT)

The proton pencil beam scanning (PBS) followed the single en-face beam technique, as described in Depauw and colleagues [47•]. Delineation of planning volumes followed an approach similar to that for conventional photon therapy. A total of 42.4 Gy (relative biological effectiveness (RBE)) was prescribed to the chest wall and all nodes. (Fig. 3) Relative biological effectiveness corresponds to the absorbed dose of x- or g-rays (Gy)-to-(Gy(RBE)) of the modality ratio to obtain the same biological endpoint. The RBE value for protons is considered to be 1.1. The Astroid™ (.decimal) treatment planning software with multi-criteria optimization capabilities was used. A unique PBS field is used at a given gantry angle (30 degrees from vertical). Beam spots were placed on a fixed size grid, extending 15 mm around the assigned target volume, with spots spaced at 1 sigma (spot size). In depth, scanning layers were spaced by 0.8x the distal 80% Bragg peak width. Due to machine limitations, a 35-mm range shifter was used to appropriately reach the superficial targets. A machine with a 3- to 7-mm spot size as a function of energy. Pareto-optimal plans were generated to meet the given constraints. Finally, the set of pareto-optimal plans was navigated to a desired state.

Conclusion

Although results from clinical trials evaluating hypofractionation for RNI or PMRT appear promising, with the exception of the START trials, follow-up from trials evaluating hypofractionated RNI remains relatively short. Ongoing clinical trials such as FABREC or Alliance (A221505) will provide valuable data on the safety of hypofractionation in breast cancer patients with immediate reconstruction. Hypofractionation for PMRT represents high-quality care that is not only more convenient for patients but also more cost-effective for the healthcare system.

Compliance with Ethical Standards

Conflict of Interest Alice Ho reports grants from Merck & Co., grants from GSK, Inc., personal fees from Amgen, outside the submitted work.

Oluwadamilola Oladeru reports grants from Radiation Oncology Institute, outside the submitted work.

Samantha A. Dunn, Nicolas Depauw, and Liam T. Vanbenthuysen 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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- • Of importance
- •• Of major importance

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