Review Article

Postmastectomy radiation: an evolution

Brianna M. Jones[1], Virginia W. Osborn[2]^

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Elmhurst Hospital, Icahn School of Medicine at Mount Sinai, Queens, NY, USA

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Correspondence to: Virginia W. Osborn, MD. Director, Radiation Oncology, Elmhurst Hospital, 79-01 Broadway, Elmhurst, NY 11373, USA.
Email: vwosborn@gmail.com.

Abstract: Postmastectomy radiation therapy (PMRT) has long been utilized to improve locoregional control versus surgery alone, and recent decades have revealed a survival benefit for many higher risk patients based on tumor or nodal factors. During this time the landscape of cancer treatment has evolved towards less invasive surgeries and more effective chemotherapy—likewise, more precise methods of delivering radiation therapy have also emerged, drastically reducing the risk for significant side effects compared with cruder historical techniques. This paper will discuss modern era radiation techniques, toxicity profile, and reconstructive options. Several recent studies have demonstrated improved locoregional control and overall survival in patients whom received postmastectomy radiation. This review will pay special attention to utility of radiation after mastectomy in patients with positive nodes and negative nodes with high-risk features. The indications for radiation therapy after mastectomy have broadened over the past few decades and this review article hopes to explore evolving evidence, as well as, new considerations in setting of increasing use of neoadjuvant chemotherapy and trend towards shorter course radiation treatment. Future directions and ongoing trials exploring benefit of additional radiation and omission of radiation will also be discussed. While some questions remain unanswered on exactly who is likely to benefit, anyone with a large tumor, nodal involvement or other high-risk features should be considered for evaluation.

Keywords: Radiation; postmastectomy; breast

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History of postmastectomy radiation therapy (PMRT)

PMRT has been used in conjunction with surgery for decades to achieve locoregional control of breast cancer. It has been used to eliminate occult or microscopic disease present after surgery in attempt to reduce risk of locoregional recurrence and improve overall survival (OS). Early randomized trials demonstrated improvements in locoregional control, but not distant recurrence or OS particularly in the setting of suboptimal chemotherapy regimens and radiation protocols.

The inferiority of earlier chemotherapy regimens that did not demonstrate a survival benefit with PMRT is reflected in the high distant failure rates seen, approximately 40% (1,2). Additionally, antiquated two-dimensional (2D) radiation techniques and field design (*Figure 1*—diagram of reverse hockey stick plan) used in these early studies were based on X-ray imaging alone (3) and thus exposed large volumes of heart and lungs to radiation, undoubtedly contributing to equivalent or

^ ORCID: 0000-0001-8700-4861.

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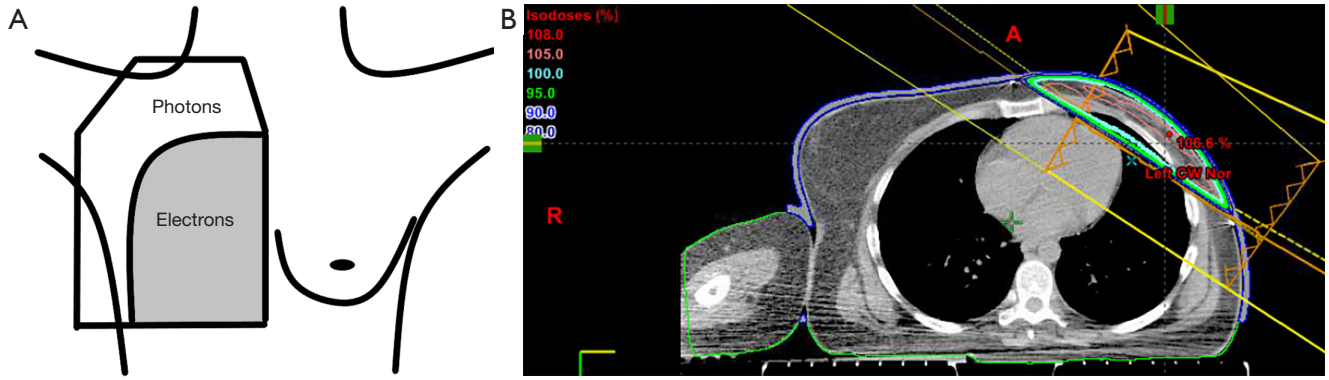

Figure 1 Examples of treatment planning techniques. (A) Diagram of reverse hockey stick radiation technique plan using a combination of photons and electrons with 2D radiation therapy. Two opposed anterior and posterior photon fields (white) used to cover axillary, supraclavicular, infraclavicular nodes, and lateral chest wall and one anterior electron field (gray) to cover medial chest wall and internal mammary nodes. (B) Modern era treatment-planning with 3D-conformal radiation therapy. In this figure two opposed tangential fields are used to cover the chest wall. Isodose lines specify percent of prescription dose coverage; 100% in light blue, 95% isodose lines in green.

worse survival outcomes. Contemporary systemic therapy regimens have demonstrated better distant control and modern radiation techniques have minimized dose to heart, lungs, and contralateral breast.

In 2001, American Society of Clinical Oncology (ASCO) consensus guidelines for PMRT recommended routine use of PMRT in higher risk patients defined as presence of four or more positive nodes (N2) and patients with T3N0 or operable clinical stage III patients (i.e., tumors >5 cm in size and 1 or more nodes with metastases). The expert panel concluded there was insufficient evidence to support radiation in T1–T2 tumors with 1–3 involved nodes, and patients with other adverse pathologic features [e.g., lymphovascular invasion (LVSI), high grade]. Additionally, there was controversy in regards to inclusion of internal mammary nodes (IMNs) in the setting of regional nodal irradiation (4). More recent randomized and nonrandomized trials demonstrated a clear benefit of PMRT in patients with any nodes positive (5). Other studies also showed minimal toxicity with coverage of IMNs (6).

More recently, ASCO's 2016 consensus guidelines updated recommendations to include patients with 1–3 positive axillary nodes. Expert panel also specified inclusion of supraclavicular (SCV), axillary, and IMNs in setting of regional nodal irradiation (7). Current National Comprehensive Cancer Network (NCCN) guidelines suggest PMRT be considered in setting of positive nodes, tumor >5 cm, positive or close margins (re-excision preferred), central/medial tumors, or tumors >2 cm with other high-risk features (i.e., young age or extensive LVSI). At the same time NCCN guidelines now reflect the more conservative recommendation of PMRT only for certain T3N0 tumors, with consideration based on high-risk features such as young age or extensive LVI (8). There are ongoing controversies about what populations can safely omit radiation and new controversies in terms of how to manage patients who receive neoadjuvant chemotherapy (NAC), which this review article will explore.

Rationale

Lymph node positive disease

Historically, radiotherapy was routinely delivered after mastectomy for women with involved lymph nodes based on early studies showing improvement in locoregional control (9,10). This practice was later brought into question, however, particularly when Cuzick and colleagues published a meta-analysis in 1987 of 7,941 patients who underwent mastectomy followed by observation *vs.* radiotherapy which showed an improvement in breast cancer cause-specific survival, but an excess of overall mortality in the radiotherapy cohort (11). The South-Eastern Cancer Study Group (SEG) subsequently found a trend towards reduction in locoregional recurrence, but no difference in survival in patients with four or more positive lymph nodes (12). The modern era has also seen drastic increases in utilization and efficacy of systemic therapy, and for a time PMRT fell out of favor, until more contemporary landmark trials from the Danish Breast Cancer Cooperative Group (DBCG) and

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Table 1 Landmark randomized controlled trials supporting use of PMRT

Trial	N	Years	Follow-up	Menopausal status	Chemotherapy	OS			LRR		
						MRM (%)	MRM + RT (%)	P value	MRM (%)	MRM + RT (%)	P value
British Columbia	318	1979–1986	20	Pre	CMF	37	47	0.03	28	10	0.002
DBCG 82b	1,708	1982–1989	15	Pre	CMF	45	54	<0.001	32	9	<0.001
DBCG 82c	1,460	1982–1990	10	Post	Tamoxifen*	36	45	0.03	35	8	<0.001

*, tamoxifen required for only 1 year in DBCG 82c. PMRT, postmastectomy radiation therapy; OS, overall survival; LRR, locoregional recurrence; MRM, modified radical mastectomy; RT, radiation therapy; CMF, cyclophosphamide, methotrexate, and fluorouracil; Pre, premenopausal; Post, postmenopausal.

British Columbia demonstrated reduction in locoregional recurrence and improved OS (*Table 1*).

The DBCG 82b phase III trial enrolled 1,708 premenopausal women with high-risk pathologic features defined as one or more of the following: involvement of axillary lymph nodes, tumor size of >5 cm, invasion of cancer to skin or pectoral fascia. Patients were randomized to receive adjuvant radiotherapy plus cyclophosphamide, methotrexate, and fluorouracil (CMF) or CMF alone following total mastectomy and axillary node sampling (13). The Danish 82c trial randomized 1,375 high-risk postmenopausal women who underwent total mastectomy with partial axillary node dissection to tamoxifen alone or tamoxifen with PMRT (14). Radiation in both these trials was delivered to the chest wall and ipsilateral regional lymphatics (including SCV/infraclavicular, axillary, and IMNs at the first four intercostal spaces) to a dose of 48 Gy in 22 fractions or 50 Gy in 25 fractions. Both the DBCG 82b/c trials showed improvement in locoregional failure and OS (*Table 1*). A major criticism of both Danish trials was concern for inadequate axillary dissection and/or pathologic analysis given only a median of seven axillary nodes were removed. However, in a pooled reanalysis of a subset of patients in 82b/c trial in node positive patients who had eight or more lymph nodes dissected there was a significant reduction in 15-year loco-regional failure rate (27% to 4%, P<0.001; 51% to 10%, P<0.001) and survival benefit (57% to 48%, P=0.03; 21% *vs.* 12%, P=0.03) in patients with 1–3 positive nodes and patients with 4+ positive nodes (15). The British Columbia trial initiated in 1979 randomized node-positive premenopausal patients treated with modified radical mastectomy with axillary lymph node dissection of levels I and II (median of 11 lymph nodes resected) and adjuvant chemotherapy to PMRT or observation, and found statistically significant improvements in 20-year locoregional recurrence, disease free survival, and breast cancer specific survival, and OS (*Table 1*). Moreover, improvement in all survival outcomes with radiation in patients with one to three axillary lymph nodes involved was similar to patients with four or more lymph nodes involved (16,17). Radiation was delivered with 37.5 Gy in 16 fractions to chest wall, SCV, axillary, and bilateral IMNs. An additional collaborative analysis of prospective data from British Columbia and M.D. Anderson Cancer Center showed that in patients with 1–3 nodes a >0.20 involved nodal ratio regardless of number of nodes removed predicted risk of locoregional recurrence exceeding 20% (18). The results of these studies supported regional radiotherapy for high-risk patients who underwent mastectomy including tumor size of >5 cm, invasion of skin/pectoral fascia/chest wall, and any positive axillary lymph nodes.

In 2005, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis included 8,500 women who underwent mastectomy, axillary dissection and node positive disease enrolled in trials of radiotherapy (chest wall and regional lymph nodes). The meta-analysis found improvement in not only local recurrence at 5 years (23% *vs.* 6% with reduction 17%), but also breast cancer specific survival (60.1% *vs.* 54.7%). In consideration of less effective chemotherapy and outdated radiation techniques, EBCTCG concluded that there is a benefit in high-risk patients but PMRT remained controversial in low nodal burden populations (19).

In 2014, newer EBCTCG meta-analysis data demonstrated improvement in local control, overall control, and OS in patients with 1–3 nodes. This large meta-analysis of 22 randomized trial showed that for women with axillary dissection (including levels I and II and/or at least 10 axillary nodes removed) and four or more positive nodes, radiotherapy reduced locoregional recurrence [two-sided

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Table 2 Important trials supporting use of PMRT in lymph node positive (pN+) breast cancer patients

Trial	N	Years	Follow-up (years)	BCM			Any recurrence			LRR		
				No RT (%)	RT (%)	P value	No RT (%)	RT (%)	P value	No RT (%)	RT (%)	P value
EBCTG meta-analysis (pN+)	3,131	1964–1986	10	66.4	58.3	0.001	62.5	51.9	<0.00001	26.0	8.1	<0.00001
EORTC 22922*	4,004	1996–2004	10.9	14.4	12.5	0.02	22.9	19.4	0.015	9.5	8.3	–

Any recurrence defined as any first breast recurrence which includes local/regional recurrence, distant progression, second ipsilateral breast cancer or death due to breast cancer. *, in EORTC 22922, only 955 patients underwent mastectomy and a separate subanalysis of outcomes not performed. PMRT, postmastectomy radiation therapy; BCM, breast cancer mortality; LRR, locoregional recurrence; RT, radiation therapy; DNR, did not report.

significance level (2P) <0.00001], overall recurrence [rate ratio (RR) 0.79, 95% CI: 0.69–0.90, 2P=0.0003], and breast cancer mortality (RR 0.87, 95% CI: 0.77–0.99, 2P=0.04) (5). Radiation reduced locoregional recurrence, overall recurrence and breast cancer specific mortality even for patients with one node positive. The EBCTCG reported that adjuvant radiation therapy (RT) following mastectomy and axillary dissection improved locoregional control at 10 years by 17.9% and reduced breast cancer mortality at 20 years by 8.1% in women with 1 to 3 positive lymph nodes.

Currently, the available randomized and non-randomized data suggests an approximately 60–70% decrease in the risk of loco-regional recurrence and a small decrease in cancer specific mortality with the addition of adjuvant PMRT in women with 1–3 nodes positive. Controversies remain related to radiation treatment recommendations in this setting including the relatively high local failure rate, up to 26–35% in the Danish and British Columbia studies and 20.3% in the EBCTCG report. However, the European Organization for Research and Treatment of Cancer (EORTC) 22922 trial looked at node positive and high-risk node negative patients with modern era techniques and still found a 1.2% reduction in locoregional recurrence and 3% increase in distant disease-free survival (DFS). These analyses show that many patients with one or more positive nodes benefit from PMRT. Whether this benefit extends to all patients, including hormone positive patients, is being investigated in MA39 (TAILOR RT) trial (20).

A summary table of trials supporting the use of PMRT in lymph node positive patients can be found in *Table 2*.

Lymph node negative disease

Retrospective analysis of DBCG 82b/c and British Columbia trials have demonstrated certain patient populations that have higher local recurrence rates and may therefore derive more benefit from supplemental external beam RT (21). High-risk patients were defined as having involvement of axillary lymph nodes, tumor size of >5 cm, invasion of cancer to skin or pectoral fascia in these trials. A multivariate analysis found size of primary tumor, frequency and number of positive lymph nodes, histopathologic grade, use of radiotherapy, and age were all significant predictors of outcome (recurrence or death) (15). In an observational study of 94 patients with pT1–2 pN0 with positive surgical margins there was a trend towards higher locoregional relapse rates (~20%) in patients who did not receive PMRT and had at least one of the following additional clinicopathologic factors: age ≤50 years, T2 tumor size, high-grade disease, or LVSI (22). Another randomized controlled trial found improved recurrence-free survival and OS in stage I–II triple negative breast cancer patients who received total mastectomy and partial axillary dissection followed by adjuvant radiation and chemotherapy compared to chemotherapy alone (23).

There is also a retrospective analysis of 1,136 node-negative T1–2 breast cancer patients treated with total mastectomy and axillary node dissection without PMRT at Massachusetts General Hospital that found tumor size ≥2 cm, close margins defined as ≤2 mm or positive margins, LVSI, age ≤50, and omission of systemic therapy were associated with higher locoregional recurrence risk (LRR) (24). The 10-year cumulative incidence of LRR for patients with no risk factors was 2.0% *vs.* 19.7% in patients with three or more risk factors.

More recent studies with modern radiation techniques and systemic therapy including MA-20 and EORTC 22922 have also supported adjuvant breast/chest wall and regional node irradiation (medial SCV, IMN, apical axillary nodes).

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Table 3 Important randomized controlled trials supporting use of RT in lymph node negative (pN0) patients

Trial	N	Years	Follow-up (years)	DFS			OS		
				No RT (%)	RT (%)	P value	No RT (%)	RT	P value
EORTC 22922	4,004	1996–2004	10.9	72.1	69.1	0.04	80.7	82.3	0.06
MA-20*	1,832	2000–2007	9.5	77.0	82.0	0.01	81.8	82.8	0.11
Fourth Military Medical University (China)**	681	2001–2006	7.2	74.6	88.3	0.02	78.7	90.4	0.03

*, MA-20 was not a PMRT trial, but still informs radiation in lymph node negative patients. **, Fourth Military Medical University investigated triple negative stage I–II breast cancer patients with 86.1% being node negative. RT, radiation therapy; DFS, disease-free survival; OS, overall survival.

MA-20 only included patients who underwent breast-conserving surgery and axillary lymph node dissection and were node positive as well as high-risk node negative patients. High-risk features were defined as tumor measuring ≥5 or ≥2 cm with fewer than ten axillary nodes removed and at least one of the following: grade 3, ER negative, or LVSI. The investigators found that receipt of regional nodal irradiation conferred a DFS benefit (25). Although not a PMRT study *per se*, the results are nonetheless important to consider regarding the potential benefit of regional nodal RT in postmastectomy patients, since the surgical treatment of nodal regions in question may not differ significantly between breast conservation and mastectomy. The EORTC 22922 trial included 24% patients who underwent total mastectomy and axillary lymph node dissection followed by radiation +/– regional nodal irradiation was comprised of node negative patient with high-risk features (central/medial tumors) and node positive patients. At 10 years, additional regional nodal irradiation resulted in significantly improved breast cancer mortality rate (12.5 *vs.* 14.4%, P=0.01), improved DFS (72% *vs.* 69%, P=0.04) and a trend toward improved OS (82.3 *vs.* 80.7%, P=0.06) (26).

The identification of high-risk node negative patient populations continues to evolve, but PMRT should certainly be considered in central/medial tumors, tumors >5 cm, T1–2 disease with other adverse clinicopathologic features (e.g., age ≤50 years, high-grade disease, triple negative histology, or LVSI), and positive margins.

A summary table of trials supporting the use of PMRT in lymph node positive patients can be found in *Table 3*.

Impact of NAC

There are currently no randomized clinical trial data to guide management of patients who receive NAC. We know that pathologic complete response (pCR) is prognostic for improved OS (27). There are open trials including National Surgical Adjuvant Breast and Bowel Project (NSABP) B51 which aims to evaluate role of regional radiotherapy in patients with pCR.

In a combined analysis of NSABP B18 and B27, Mamounas and colleagues examined locoregional recurrence after NAC in patients who did not receive regional radiotherapy. In the mastectomy cohort, 10-year cumulative incidence of locoregional recurrence was 12.6%. On multivariate analysis, there were five factors associated with LRR including: age, clinical tumor size >5 cm, clinically positive nodes, pCR in nodes but no pCR in breast, and pathologically positive nodes after NAC (28). In a pooled analysis from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC), tumor subtype and pathologic response were independent predictors of locoregional recurrence. Specifically, triple negative patients had three times the 5-year cumulative incidence of LRR compared to hormone receptor positive, grade 1–2 patients. In the phase III EORTC 10994 trial, multivariate analysis of LRR following neoadjuvant therapy found luminal A subtypes had the lowest rate of recurrence compared to triple negative and patients achieving pCR had the lowest rate of recurrence compared to those with residual disease in breast and nodes after NAC (29). Another retrospective analysis at M.D. Anderson found patients with clinical T3N0 disease treated with NAC and mastectomy, but without PMRT had significantly elevated risk of LRR when compared to patients who received PMRT (30).

The role of PMRT is controversial for patients with clinical lymph node positivity who subsequently achieve a complete response in the axilla, and multiple studies have failed to demonstrate a significant benefit in clinical stage II (cT2–T3, cN1) patients with pCR after NAC (31,32).

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In their 2012 study, Fowble and colleagues quantified the risk of recurrence in women who underwent NAC followed by mastectomy but who did not undergo PMRT (33). In this study, women with pCR following NAC had a low rate of local regional recurrence (3%). While this showed no recurrences (0%) in women with HR+/Her2–/HR–/Her2–/HR–/Her2+ disease and a higher risk for recurrence among women with HR+/Her2+ (14%) disease, the overall numbers from this study were small and the role of RT in this setting remains uncertain.

Huang and colleagues at M.D. Anderson Cancer Center performed a meta-analysis of six prospective NAC trials and found post-mastectomy radiation and regional nodal irradiation improved 10-year cause specific survival in locally advanced breast cancer including: clinical stage IIIB or higher, T4, N2–3, four or more pathologically positive nodes (ypN2). Locoregional recurrence rate was reduced from 22% to 11% with PMRT and patients with cT3–4 tumors, stage IIB or greater, ypT2 or greater, and ypN2 or greater demonstrating significant benefit (34).

Current indications for consideration of PMRT in setting of NAC include axillary node involvement after systemic therapy (ypN+), residual breast disease (ypT+), cT3–4, or above cN2–3 disease. There is less evidence to guide management of patients with cN1 disease that become ypN0 and stage I–II (except T3N0) after chemotherapy. NSABP B51 RTOG 1304 seeks to elucidate which of these patients benefit from radiation. Observation may be indicated for patients with clinically small volume of disease, pCR in breast and nodes or residual T1 luminal subtype and older age (35).

Treatment techniques

Standard fields

There has been an immense evolution of modern radiation techniques transitioning from two-dimensional field to three-dimensional computed tomography (CT) planning. Standard post-mastectomy radiation is typically delivered using photons with forward planning technique termed 3D conformal radiation therapy (3DCRT). Chest wall irradiation alone typically involves two opposed tangential fields. In order to treat chest wall and regional nodes 3 to 4 fields are typically used: two opposed tangential fields, one anterior oblique SCV field and often a posterior/oblique field which can increase deep SCV & axillary coverage. Sometimes a separate anterior IMN field is also added, when clinically appropriate (see IMN section below). Different beam angles, field sizes, beam energies, and weighting are then employed to create an optimal treatment plan. Deep inspiratory breath-hold (DIBH) is a technique whereby patients are treated during inspiration and is routinely used to minimize heart dose, particularly in left sided breast cancer, as well as ipsilateral and total lung dose. Pulmonary and cardiac toxicity are minimized with shielding by multi-leaf collimators. A chest wall bolus comprised of tissue-equivalent material is often used to increase skin dose in higher risk patients. A 0.5–1-cm bolus may be applied every day or every other day, for example.

Conventional dose and fractionation for PMRT is 50–50.4 Gy in 1.8–2.0 Gy per fraction in 25–28 fractions to the chest wall. A chest wall scar boost of 10 to 16 gray in 4–8 fractions may also be employed. Although no randomized data is available to guide decisions about chest wall boost, it should certainly be considered in cases of inflammatory breast cancer or close/positive margins. Generally, clinicians aim for at least 90–95% of prescription dose coverage or around 45–50 Gy to regional nodes. Hypofractionated protocols are under investigation as described below.

IMNs

The DBCG IMN prospective cohort of 3,089 node positive breast cancer patients received radiation to the chest wall, SCV, undissected axilla and right sided cases also received IMN radiation (whereas left sided cases did not receive IMN coverage). They found at 8 years improved breast cancer mortality and OS with IMN irradiation and trend toward reduction in distant recurrence (6). More widespread coverage of IMNs has been supported by several large randomized trials with minimal toxicity. A single institution retrospective analysis 169 women treated with chest wall/breast, SCV, axilla, and IMNs. IMN radiation did not lead to unacceptable heart and lung doses with use of 3DCRT (36). Based on EORTC 22922 trial results, patients with central/medial tumors or axillary nodes should receive IMN radiation (26).

Modified wide tangent fields can be used in which opposed tangent fields are widened superiorly to include to cover age of three intercostal spaces that contain the IMNs. Alternatively, a separate anterior field can be added with either electrons or photons.

IMRT/protons

Intensity-modulated radiation therapy (IMRT) is considered when there are concerns about heart or lung

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dose or constraints are not met with conventional 3DCRT. IMRT also utilizes photons but involves more beams and an inverse planning technique whereby goals of coverage and dose constraints are entered and a treatment planning system creates an optimal plan. A potential downside of this technique is a larger area of low-dose radiation delivered to other parts of the body than with standard 3DCRT.

The use of proton beam radiation is currently under investigation. Protons have unique dose deposition characteristics in that they deposit maximum dose at specific depths in tissue (Bragg peak), minimizing entry and exit dose. The RADCOMP Consortium trial is comparing photon to proton therapy in nonmetastatic patients receiving breast/chest wall and regional node irradiation (37).

Hypofractionation

In breast conservation therapy, hypofractionated whole breast irradiation has become the standard of care (38). In setting of mastectomy, hypofractionation is still under investigation. Peking Union Medical College in Beijing, China evaluated 811 patients with T3–4 or ≥4 nodes who underwent mastectomy without reconstruction were randomized to receive conventional fractionated PMRT (chest wall, undissected axilla, SCV and IMNs) to dose of 50 Gy in 25 fractions *vs.* hypofractionated PMRT to a dose of 43.5 Gy in 15 fractions. This study showed no differences in LRR, DFS, OS, or toxicity (39). UK Fast Forward also demonstrated noninferiority of 26 Gy in 5 fractions compared to 40 Gy in 15 fractions to chest wall alone, but only 7% of the study cohort underwent mastectomy (40). The START A and B trials also showed favorable outcomes with minimal toxicity of 39 Gy in 13 fractions, 41.6 Gy in 13 fractions, and 40 Gy in 15 fractions, but again only 15% of this patient cohort received hypofractionated chest wall irradiation (41). The SUPREMO trial is ongoing and seeks to evaluate PMRT (chest wall only) in T1–2 and 1–3 nodes positive, T2N0 grade 3, or T2N0 with LVSI with choice of 40 Gy in 15 fractions, 45 Gy in 20 fractions, or 50 Gy in 25 fractions (42). Two-year follow-up results show minimal toxicity in published early analysis (43).

Of the above studies, the Beijing study is the only one to provide randomized evidence that hypofractionation of chest wall and regional nodes is noninferior in non-reconstructed patients. We await the results of the Alliance RT Charm trial that will evaluate hypofractionated PMRT in reconstructed patients (44).

For patients with prior breast augmentation, there was a recent study published by Tadros *et al.* to evaluate feasibility of hypofractionated in setting of prior breast augmentation. Seventy-one patients were retrospectively analyzed. In this group, 39.4% of patients were treated with conventionally fractionated RT, 54.9% of patients were treated with hypofractionated RT, 84.5% of patients were not treated with a third radiation field, 81.7% of patients received a breast boost, and 87.3% of patients underwent a retropectoral breast augmentation procedure. Of these 71 patients, physician rated assessment after completing RT was "Excellent" in 60.6% of cases and "Good" in 26.8% of cases. Additionally, 25.4% of patients developed a new or worsening of breast contracture after therapy and 12.7% were referred to plastic surgery for a surgical revision. There were no instances of implant-loss. On univariate analysis, implant location, time from implant to diagnosis, RT type, RT boost, body mass index (BMI), and tumor size were not associated with new or worse contracture. However, limitations of this study are its relatively short mean follow-up of 1.9 years (45). Based on retrospective studies, hypofractionation in setting of reconstruction and prior breast augmentation appears to be noninferior to standard fractionation with low toxicity, but more data is necessary in order to make definitive recommendations.

Treatment side effects

Radiation side effects are typically categorized as acute or late, with common acute effects of PMRT including dermatitis and fatigue that typically resolve in the weeks following completion. Because so many breast cancer patients go on to become long term survivors, a detailed discussion of more serious or long term (late) effects is also necessary. Lung toxicity can range from asymptomatic fibrosis within the treatment beam path or, rarely, pneumonitis. Fortunately, modern planning techniques allow for strict constraints on lung dose leading to reduced complication rates (46). Radiation-induced cardiac toxicity was a big issue historically, and a 7.4% increase in cardiac events has been reported for each 1 Gy mean heart dose (47). With CT-based planning it is now much easier to ensure that the heart is not directly within the radiation field. Notably, coincident with widespread adoption of 3DCRT was increased use of cardiotoxic systemic therapy regimens including adriamycin, taxanes, trastuzumab, and pertuzumab. Lymphedema has plagued many recipients of PMRT, but interestingly a 2020 study found on multivariate analysis that the primary risk stems from the axillary surgery itself

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rather than adjuvant treatment (48). Finally, cosmesis can always be impacted by RT, a particular concern for patients undergoing reconstruction. Clinicians should discuss the potential impact of radiation on reconstruction with these patients as it may result in contracture, fibrosis, impaired wound healing, reconstructive failure, pain and breast asymmetry (49-52). In a retrospective study of patients receiving flap reconstruction, 31.6% of patients who received radiation after reconstruction (51). While there are certainly advantages to direct-to-implant procedure, these patients have higher incidence of complications in setting of PMRT. In a study by Roostaeian and colleagues, radiation after immediate implant reconstructions had higher need for revision and lower aesthetic outcome compared to two-stage implant reconstruction (52). According to current NCCN guidelines, immediate autologous reconstruction and implant is not preferred if there is plan for radiation following mastectomy (8). As a result, tissue expanders are often placed at time of surgery and permanent implant placement or delayed autologous tissue breast reconstruction is usually deferred for approximately six months following completion of RT.

Ongoing questions and future directions

There are ongoing studies exploring omission of radiation in low-risk patients. Despite evidence from EBCTCG that T1–2 patients with 1–3 axillary nodes demonstrate a LRR reduction from PMRT, these trials reported higher local recurrence rates (21%) compared to more modern trials (4–10%) using contemporary systemic therapies and standard axillary dissection (≥10 removed nodes), which limits generalizability of these results to all patients (7). Omission of regional radiotherapy (chest wall and regional nodes) in low-risk node positive patients (i.e., age >50, ER+ and/or PR+, HER2-negative, 1–3 positive axillary nodes, oncotype DX recurrence score ≤18) is currently being investigated in CCTG MA-39 Tailor RT phase III randomized trial (20). The SUPREMO trial will also evaluate PMRT in high-risk node negative disease and early-stage disease with one to three positive nodes (43). Clinical trials will help determine whether these lower-risk patients benefit from PMRT with modern systemic therapy and surgery.

In view of increasing utilization of NAC, there remain many unanswered questions regarding role of PMRT. The NRG NSABP B-51/RTOG 1304 phase III randomized trial is evaluating benefit of regional radiotherapy in setting of upfront clinical T1–3N1 disease with no pathologic nodes positive (ypN0) after NAC with or without HER2 directed therapies and surgery. These trials will help elucidate whether radiotherapy can be omitted in favorable risk cohorts and patients with complete pathologic response to NAC. A few trials including RT Charm and SUPREMO are currently underway to evaluate whether more hypofractionated regimens can be employed for postmastectomy (chest wall and regional nodal) radiation (42,44). Additionally, incorporation of genetic and molecular information into clinical practice is under investigation. For example, I-SPY 2 uses MammaPrint to stratify patients into various systemic therapy arms (53). Several studies are also investigating more modern radiation techniques such as IMRT and proton therapy. There is certainly still controversy in role of PMRT in certain subgroups of patients, but it remains true that both surgery and radiation are vital in locoregional control.

Pearls

- ❖ PMRT is associated with reduction in locoregional recurrence and improved OS in high-risk patients including those with positive lymph nodes, tumor greater than 5 cm, skin or chest wall invasion, and node negative patients with high-risk features: ER–, triple negative histology, grade 3, LVSI, central/medial tumors, young age (≤50 years or premenopausal status), close or positive margins.
- ❖ After NAC, PMRT is likely appropriate if cT3–4, cN2–3, or residual nodal disease (ypN+) is present. Full indications for PMRT after NAC are not fully established, however, and decision-making should be shared in a multidisciplinary capacity allowing for recommendations to be individualized based on unique clinicopathologic features. In the absence of randomized evidence, PMRT should be considered in certain stage I–II (cT2, cN1) patients with high-risk factors: young age, high grade histology, triple negative receptor status, LVSI, close/positive margins, or other adverse pathologic features.

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