

Post-Mastectomy Radiotherapy

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Abstract: Between 1997 and 1999, three studies re-ignited the debate on post-mastectomy radiation therapy (PMRT). Despite 20 years of follow-up and multiple re-analyses, the results of these studies still generate vigorous debate among the learned men and women who care for breast cancer patients. In honor of the 10th anniversary of the Danish Breast Cancer Cooperative Group Post-Mastectomy trial 82c publication, the following review offers the reader a brief history of the controversies that preceded and followed these publications. Other related controversies, PMRT in the setting of neo-adjuvant chemotherapy, positive margins or T3N0 primary tumors, as well as internal mammary lymph node irradiation, are also presented. Finally, we present a brief discussion about the toxicities associated with PMRT. This review will familiarize the reader with often discussed/debated issues concerning PMRT and prepare them to enter the debate.

Introduction

This year marks the 10th anniversary of the publication of Danish Breast Cancer Cooperative Group's (DBCG) trial 82c. This seminal paper was the third in a series of publications that forever changed the discussion about post-mastectomy radiation therapy (PMRT). This and the other 2 trials, DBCG 82b and British Columbia Cancer Agency Randomized Radiation (BC) trial, were the first prospective randomized trials using uniform modern radiation techniques to show not only a local regional control advantage but also a survival advantage associated with PMRT. For reasons that will be discussed below, these papers were, and in many quarters remain, controversial. Nonetheless, they will help solidify the notion that improved local control can result in improved overall survival (OS).

Post-Mastectomy Radiation

The second most common use of therapeutic radiation in the management of breast cancer occurs after mastectomy. Some of the earliest randomized prospective trials in oncology addressed the role of radiation after mastectomy for breast cancer. Oslo I, Oslo II, and The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-02 are examples of early trials in which women with nonmetastatic breast cancer were randomized to adjuvant radiation or no radiation after mastectomy¹⁻³ (Table 1). Although the specifics

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Post-mastectomy, radiation, breast cancer, toxicity

Table 1. Early Randomized PMRT Trials

	Oslo I 1964–1967	Oslo II 1964–1972	B-02 1961–1968
# Patients	546	542	954
Fields	CW/RN	RN	RN
Energy	kV	MV	kV/MV
Systemic	Ov. Abl.	Ov. Abl.	
F/U	15 year	15 year	5 year
LRF (%)			
No radiotherapy	16	13	17
Radiotherapy	7	5	8
OS (%)			
No radiotherapy	Stage I/II 66/35	Stage I/II 71/43	62
Radiotherapy	66/35	60/41	56

Cw=Chest wall; kV=Kilovoltage; LRF=locoregional failure; MV=Megavoltage; OS=overall survival; Ov. Abl.=Ovarian Ablation; PMRT=post mastectomy radiotherapy; RN=regional nodes.

of fields irradiated, dose delivered, and systemic therapy administered differed markedly, these trials uniformly showed a statistically significant local control benefit associated with PMRT. However, no OS benefit was identified. In fact, there was a suggestion of survival detriment in B-02 (Table 1). The negative impact on survival from PMRT was further substantiated by a meta-analysis by Cuzick and colleagues.² In this meta-analysis, which included PMRT trials from 1949–1974, there was a significant decrease in 10-year OS in patients treated with PMRT (57% vs 54%; $P<.05$).² The authors updated the meta-analysis 7 years later and this time showed that although there was a numerical difference in OS at 10 years in favor of the nonirradiated group, the difference was no longer significant. The difference in OS was attributed to excess “cardiac deaths” in the irradiated patients.³ These meta-analyses were widely criticized. The studied trials spanned 3 decades. Consequently, the radiation techniques were not uniform, and many would be considered inadequate or outdated today. Additionally and importantly, there was no uniform use of systemic therapy in the trials analyzed by Cuzick and colleagues.³ Despite the valid criticisms of these meta-analyses, PMRT was generally reserved for only the most advanced cases (eg, Haagenson’s 5 grave characteristics)⁴ and mainly viewed as a means to improve local control, not survival.

Between 1997 and 1999, 3 randomized prospective trials of PMRT were published: the Danish Premenopausal and Postmenopausal trials (82b and 82c respectively) and the British Columbia trial.⁵⁻⁷ The Danish trials (1982–1989), with approximately 1,400 patients each, and the smaller Canadian trial (1978–1985), with 318 patients, randomized women treated with mastectomy and adjuvant systemic therapy to PMRT or no PMRT. The radiation fields and doses delivered were fairly uniform, and all patients received systemic therapy. As seen in the earlier studies, these modern trials showed a significant difference in local regional recurrence (LRR) rate in favor of PMRT. However, for the first time, all 3 trials also showed a significant improvement in OS, also in favor of radiation (Table 2). These trials, in contrast to their predecessors, benefited from modern standardized radiation therapy techniques, as well as modern chemotherapy.

The excitement of these results was quickly tempered by significant criticisms. There was general agreement with the results of the trials in patients with 4 or more positive lymph nodes. However, the true benefit of PMRT in patients with 1–3 positive lymph nodes was called into question because the LRR rate in the control arm was unusually high. All 3 trials had LRR rates of 30–33% at 10–15 years in patients with 1–3 positive lymph nodes who did not receive radiation. This rate is in contrast to a 10-year LRR rate of 13% in similarly staged and treated patients, as reported in retrospective reviews of prospective Eastern Cooperative Oncology Group (ECOG) and NSABP trials.^{8,9} In essence, many argued that radiation appeared more beneficial than it really would have been if the women had a LRR rate closer to 13%, as expected in the community, rather than 33%, as reported in the Danish and British Columbia trials. There are plausible reasons why the LRR rate in the PMRT trials’ control arms seemed so elevated. One possible reason is that the elevated LRR rates reported by the Danish and BC trials may be a statistical anomaly. These modern PMRT trials used Kaplan-Meier analyses, rather than cumulative incidence or crude recurrence rate analyses, as more commonly used in U.S. trials.^{8,9} However, the most commonly accepted reasons for the LRR discrepancies center on what some critics would consider the nonstandard systemic and local therapy administered in these trials.

The criticisms concerning systemic therapy involved the use of CMF (cyclophosphamide, methotrexate, 5-FU) in 2 of the trials, and tamoxifen in the third. One may argue that the results of these PMRT trials are not applicable to today’s breast cancer patient because 1) CMF is no longer the most common first-line chemotherapy regimen in breast cancer and 2) tamoxifen was administered without knowledge of the patients’ estrogen/progesterone receptor (ER/PR) status and was prescribed for only

Table 2. Modern PMRT Trials

	BC (1978– 1985)	D 82b (1982– 1989)	D 82c (1982– 1989)
# Patients	318	1473	1460
Eligibility	N+	T3-4 or N+	T3-4 or N+
Fields	CW & RN	CW & RN	CW & RN
Systemic	CMF	CMF	Tamoxifen (30 mg/d -1 year)
F/U (years)	20	10	10
LRR (%)			
No radiotherapy	28	26	29
Radiotherapy	10	5	4
OS (%)			
No radiotherapy	37	45	36
Radiotherapy	47	54	45
<i>P</i> value	.03	<.001	.03

CMF=cyclophosphamide, methotrexate, 5-FU; CW=Chest wall; LRR=local regional recurrence; OS=overall survival; PMRT=post mastectomy radiotherapy RN=Regional Nodes

1 year, as opposed to today’s recommended 5-year course. When one considers evidence that systemic therapy can also affect local control (eg, B-06, B-21), the argument that substandard systemic therapy may have affected LRR rate seems wholly reasonable.

With respect to local therapy, some have argued that inadequate surgery, specifically an inadequate axillary dissection, may be the cause of the high rate of LRR (30–33%) seen in patients with 1–3 positive lymph nodes in the Danish and British Columbia trials. The median numbers of lymph nodes removed were 7 and 11 in these trials, respectively. In contrast, the median numbers of lymph nodes removed in the retrospective analyses of ECOG and NSABP trials, both of which reported a 13% LRR rate, were 15 and 16, respectively.^{8,9} The extent of axillary surgery has been shown to have a local therapeutic benefit.⁹ With that in mind, some concluded that the radiation in the modern PMRT trials compensated for less-than-ideal surgery, and thus the benefit of radiation in these trials is exaggerated for patients with 1–3 positive lymph nodes. It is this belief that prevents many physicians from offering PMRT to breast cancer patients with 1–3 positive lymph nodes.¹⁰

A large phase III trial, in which women with 1–3 positive lymph nodes after mastectomy were randomized

Table 3. Modern PMRT Trials by Number of Lymph Nodes

	BC No RT/RT	D82b No RT/RT	D82c No RT/RT
LRR(%)			
N0	NA	17/3 <i>P</i> <.05	23/6
1–3	33/13 <i>P</i> <.05	30/7 <i>P</i> <.05	31/6
4+	46/21 <i>P</i> <.05	42/14 <i>P</i> <.05	46/11
OS (%)			
N0	NA	70/82 <i>P</i> <.05	56/55
1–3	53/64 (NS)	54/62 <i>P</i> <.05	44/55
4+	28/35 (NS)	20/32 <i>P</i> <.05	17/24

LRR=local regional recurrence; NA=not applicable; OS=overall survival; PMRT=post mastectomy radiotherapy; RT=radiotherapy

to irradiation or no irradiation, opened in the United States. The hope was that this trial would end the controversy concerning PMRT in this group of patients. Unfortunately, due to poor patient accrual, the trial was closed prematurely. Trials such as the United Kingdom’s Selective Use of Postoperative Radiotherapy after Mastectomy (SUPREMO) BIG 2-04 phase III randomized trial will evaluate the benefit of PMRT in patients with 1–3 positive lymph nodes.¹¹ Additionally, the Canadian National Cancer Institute (NCIC) M20 trial is evaluating the benefit of nodal radiation in women undergoing breast conserving therapy. A similar trial is underway in Europe (EORTC 22922).¹² It will be several years before the results from these ongoing trials help to answer questions concerning PMRT for women with 1–3 positive lymph nodes.

There is literature available now that suggests that the controversy over whether or not to offer PMRT to patients with 1–3 positive lymph nodes may soon be ending. First, the authors of the Danish trials, in response to criticisms concerning the number of nodes removed, re-analyzed their data by evaluating patients who had more than 8 nodes removed. In this re-analysis, the authors again reported a statistically significant OS benefit in favor of PMRT in patients with 1–3 positive lymph nodes (48% vs 57% at 15 years *P*=.03).¹³ Secondly, in 2006, the Early Breast Cancer Trialists’ Cooperative Group (EBCTCG) presented the results of a meta-analysis of more than 3,000 women with pathologically proven

breast cancer, treated with mastectomy and axillary clearance, who had 1–3 positive lymph nodes and were randomized to adjuvant radiation or no radiation. The majority of the patients received systemic therapy. In this meta-analysis the authors reported an absolute reduction in breast cancer mortality and all-cause mortality with PMRT of 7.6% (log rank $2P=.002$) and 5.3% (log rank $2P=.05$), respectively.¹⁴ Thirdly, perhaps most intriguing is a review of the Surveillance, Epidemiology and End Results (SEER) database by Buchholz and associates.¹⁵ The authors compared 12,693 patients with 1–3 positive lymph nodes treated with lumpectomy and radiation with 18,902 similar patients treated with mastectomy without radiation. This analysis, with limited radiation details and subject to the common critiques of retrospective studies, revealed a 15-year breast cancer specific survival benefit in favor of the irradiated group (80% vs 72%; $P<.001$). On Cox regression analysis, modified radical mastectomy (MRM) without RT was associated with a mortality hazard ratio (HR) of 1.25 ($P<.001$). When one considers these reports, it is reasonable to agree with the concluding statement in an editorial by Marks and coworkers, “It is time that we dispense with the artificial partitioning of patient groups with 1–3 versus 4 or more positive lymph nodes”.¹⁶ Clearly, as stated in the above editorial, relying on simply the number of positive lymph nodes may oversimplify the process by which we predict LRR and by extension the need for PMRT. To that point, there is literature to suggest that the number of positive lymph nodes in relation to the total number of nodes resected is more predictive of LRR risk than simply the number of positive lymph nodes alone.¹⁷⁻¹⁹

It is likely that other factors can aid in predicting LRR risk after mastectomy. For example, researchers have shown that the 21-gene recurrence score assay (Oncotype DX), commonly used to determine the risk of distant recurrence, may also be predictive of the risk of LRR.²⁰ Other factors reported to be associated with increased local regional failure (LRF) include tumor size, positive margins, extracapsular extensions, lymphovascular invasion (LVI), response to neoadjuvant chemotherapy (NAC), age, ER/PR status, and p53 over-expression.^{5,8,9,21-25} While we await evaluation of putative biologic, genetic, and clinical factors predictive of LRR such that we can judge a patient’s need for PMRT, it is perhaps prudent to seriously consider PMRT for women with 1–3 positive axillary lymph nodes.

Neo-Adjuvant Chemotherapy and PMRT

The main benefits of primary or NAC are its ability to increase a woman’s chance for breast conservation and to

provide in vivo chemo-sensitivity information.^{26,27} The resulting popularity of NAC has raised several questions for radiation oncologists concerning the use of PMRT. The estimation of LRR was based on clinical and pathologic factors identified perioperatively (eg, Haagensen’s 5 grave characteristics or clinical TNM staging) or postoperatively (extent of tumor, number of positive lymph nodes, etc). Importantly, the estimated risk of LRR was informed by clinicopathologic factors from heretofore undisturbed/untreated tumor (ie, prior to any systemic therapy). With the advent of NAC, and the resulting shift in treatment sequence, the peri- and postoperative clinicopathologic information obtained is no longer from an undisturbed/untreated tumor. Consequently, the ways in which clinicopathologic factors are used to predict LRR may need to be reassessed. A typical conundrum would be the patient with positive lymph nodes prior to NAC, but at the time of mastectomy had no identifiable nodal metastases. Should this pathologic N0 patient be offered PMRT?

Most of the U.S. literature for PMRT in the setting of NAC is derived from 2 prospective randomized trials, NSABP B-18 and B-27, and serial retrospective studies from MD Anderson Cancer Center (MDA).^{26,28-33} In study B-18, patients were randomized to either pre- or postoperative doxorubicin and cyclophosphamide (AC).³³ In study B-27, patients were randomized to preoperative AC, preoperative AC followed by preoperative paclitaxel or preoperative AC followed by postoperative paclitaxel.²⁸ For the purpose of discussion, it is perhaps best to consider the risk of LRR, and thus the need for PMRT, first as a function of clinical stage at presentation and secondly, according to pathologic nodal status at the time of surgery. Patients with inflammatory breast cancer are not included in this discussion.

Data on patients with clinical stage I/II disease are limited, and thus the recommendations concerning PMRT in this group should be viewed judiciously. MDA retrospectively reviewed 542 patients from 1974–2000 who were treated with NAC, mastectomy, and PMRT and compared them to 134 patients similarly treated but without radiation.³⁴ In patients with clinical stage I (n=1) or IIA (n=29) breast cancer, there was no significant difference in LRR at 10 years between those who did and did not receive PMRT. However, in patients presenting with clinical stage IIB or greater disease (n= 646), there was a significant decrease in LRR at 10 years with PMRT (11% vs 26% $P<.001$).³⁴ This report would suggest that simply based on stage at presentation, patients with clinical stage IIB disease or greater should receive PMRT after NAC.

However, it is important to ask whether the benefit of PMRT still exists in patients who have had a pathologic complete response or are node negative at time of

surgery. Based on NSABP B-18/27 and retrospective trials from MDA, patients who were clinical stage II prior to NAC, were pathologically node negative at time of mastectomy, and did not receive PMRT, had a LRR rate of less than 10% at 8 years.³⁰ Huang and colleagues from MDA studied clinical stage I–II patients who achieved a pathologic complete response. They showed that there was no significant difference in LRR between those that did or did not receive PMRT.³⁴ MDA also reported that women who were clinical stage III prior to NAC were pathologically lymph node negative at mastectomy and did not receive PMRT had a 10-year LRR rate of 33%.^{32,34} Unlike clinical stage II patients who were node negative at mastectomy, the LRR rate in these clinical stage III patients significantly decreased with the addition of PMRT.^{31,32,34} It is important to note here that an analysis of NSABP B-18/27 data also revealed that patients with any residual nodal disease after NAC have a “clinically significant” 15% risk of LRR, and therefore, may benefit from PMRT.³⁰

Although the data presented here are limited and partly based on retrospective studies from a single institution, some generalized observations/recommendations can be made. Women who have clinical stage II disease prior to NAC and are pathologically node negative at the time of mastectomy appear to have a risk of LRR insufficient to warrant routine use of PMRT. However, patients with clinical stage III disease prior to NAC (regardless of ultimate nodal status) and patients with positive lymph nodes after NAC have a LRR rate sufficiently high to warrant serious consideration of PMRT. Additional prospective randomized trials are needed to further evaluate the role PMRT in the setting of NAC. Until this is possible, it is incumbent upon completed and currently open NAC trials to also collect and report LRR data.

Positive Margins

With the exceptions of inflammatory breast cancer and NAC, the role of PMRT in women without nodal metastases remains less well defined. Arguably, the 2 most discussed/debated clinical indications for PMRT in node-negative women are 1) a positive margin after mastectomy and 2) a primary tumor 5 cm or larger (T3). First, principles would suggest that women with close or positive margins after mastectomy are likely to have residual tumor burden greater than patients with negative margins. This presumed greater tumor burden is expected to increase the risk of LRR, and thus, the patient should be offered PMRT. While this logic is prevalent and sound, there is literature to suggest that not all women with positive mastectomy margins have LRR rates that warrant PMRT.

Ahlborn and coworkers studied 346 node-negative women treated with mastectomy without PMRT. Patients were divided into those having a close (<4 mm) or not close (>4 mm) fascial margin.³⁵ The authors were unable to show a significant difference in LRR with respect to margin status (6% vs 3% at 4 years). Adjuvant radiation did not appear to make a difference in LRR, as detailed in a study by Truong and associates of 94 women with positive mastectomy margins (ink on cancer cells).³⁶ In that study, 41 of 94 patients received PMRT. With a median follow-up of 7 years, there was no significant difference in LRR between those who did and did not receive radiation (5% vs 11%; $P>.05$). Patients in the irradiated arm were more likely to receive chemotherapy, whereas hormonal therapy was equivalent in both arms. On multivariate analysis, there was a trend towards increased LRR in women with positive margins and an age of 50 years or less (20%). Jagsi and colleagues reported on a series of 870 node-negative breast cancer patients treated with mastectomy without radiation.³⁷ In this study, 64 patients with close (<2 mm) or positive margins (0 mm) were compared to 584 patients with negative mastectomy margins (≥ 2 mm) and 151 with unknown margins. Approximately one third of the patients received systemic therapy. In contrast to the above, these authors reported a significant increase in the 10-year LRR in patients with positive or close deep margins (21/22% vs 5%; $P=.001$).

Freedmen and coauthors reviewed the rate of chest wall recurrences in 22 node-negative women with tumors smaller than 5 cm and close (<5 mm) or positive mastectomy margins.³⁸ In this population, none of whom received PMRT and majority of whom received systemic therapy; the chest wall recurrence (CWR) rate at 8 years was 18%. Interestingly, the CWR rate for patients 50 years or younger and with 0–3 positive lymph nodes was 28% compared to 0% in patients older than 50 years ($P=.04$). Katz and associates reviewed 29 patients with close (<5 mm) or positive MRM margins, tumors less than 5 cm, and stage II–IIIA disease lymph nodes.³⁹ The authors reported a 45% LRR rate at 10 years, which was independent of age. It is unclear how many of these margin-positive patients were node negative. Since the data on this topic are limited and complicated by the retrospective nature of the studies, the varying definitions of close/positive margins, and the lack of details about the location of the margins in question, a definitive recommendation about the need for PMRT in these node-negative patients cannot be made.

T3N0 Disease

Approximately, 0.5–4% of breast cancer patients present with primary tumors greater than 5 cm, yet are node

negative at the time of mastectomy.⁴⁰⁻⁴⁵ Today, it is common for patients with large primaries to be treated with NAC. Until recently, and in the non-NAC setting, these patients were thought to have a high rate of LRR and, therefore, were routinely offered PMRT. For example, the Danish PMRT trials 82b and 82c included women who had a T3 primary or skin/chest wall involvement, yet were also node negative.^{5,6,22} The 82b trial reported a difference in the 10-year LRR rate in patients treated with and without radiation of 3% and 17% ($P < .05$), respectively. MDA retrospectively reviewed patients treated with mastectomy and doxorubicin-based chemotherapy without irradiation. They reported a 10-year LRR rate of 29% (3/7) in patients with T3N0 disease.⁴¹ Given the previously discussed criticisms of the 82b and 82c trials and the small number of patients in the MDA study, it is easy to see why there was ambivalence in treatment recommendations, as reflected in the consensus papers of the time.^{44,46,47}

With recent publications, treatment recommendations for patients with T3N0 disease may become clearer. Floyd and colleagues studied 70 patients who had tumors greater than or equal to 5 cm (26% >7 cm), were node negative, and were treated by mastectomy without RT.⁴⁰ Fifty-six percent received systemic therapy. These authors reported a 5-year LRR rate of 7.6%. Taghian and coworkers studied 313 node-negative patients with tumors greater than 5 cm (12% >7 cm) and treated on 5 prospective NSABP trials.⁴⁴ All patients were treated with mastectomy without RT, and 75% received some form of systemic therapy (hormonal or cytotoxic or both). The 10-year LRR rate in this study was 7.1%. Mignano and coauthors studied 101 patients with T3N0 disease also treated with MRM without RT.⁴³ Twenty-two percent of these patients had tumors greater than 7 cm. In contrast to the studies by Taghian and coworkers and Floyd and colleagues, only 14% of the patients received some form of systemic therapy. Nonetheless, Mignano and coauthors posted a 5-year LRR rate of only 10%. All 3 studies attempted to identify clinical and pathologic prognostic factors for LRR. In the analysis by Floyd and colleagues, LVI was significantly associated with an increased LRR. No factors were identified in the studies by Taghian and coworkers or Mignano and colleagues; however, it appears that neither study specifically tested LVI as a prognostic factor.

A study that examined cause-specific survival (CSS) and OS also suggests that RT may not be needed in this class of patient. McCammon and associates, using the SEER database, identified 1,865 women with T3N0 primary breast cancer.⁴² Thirty-four percent of the patients received PMRT. Approximately one third of the patients had tumors greater than 7 cm. These authors revealed that there was no statistically significant difference in the

10-year CSS between those that did or did not receive PMRT (81.6% vs 79.8%; $P = .38$). There was a significant improvement in OS in patients who received PMRT, but given the lack of difference in CSS, this OS difference most likely represents patient selection. Thus, when one considers the recent large retrospective studies above, in which a significant proportion of patients had tumors larger than 7 cm, there does not appear to be strong evidence to routinely offer PMRT to women with T3N0 breast cancer.

Internal Mammary Lymph Node Controversy

Once the decision is made to offer PMRT, few topics generate discussion more vigorous than the topic of whether or not to treat the internal mammary lymph nodes (IMLNs). This state of affairs arises from not only confusion over the benefit of treating these nodal areas, but also from fear of potential complications. Arguably, the most feared complication is cardiac morbidity.

Those opposed to IMLN RT frequently cite prospective randomized data in which extended radical mastectomies, including IMLN dissections, were compared to mastectomies, in which the IMLNs were not dissected.^{48,49} The outcomes were similar in both groups. These trials are somewhat flawed as they were not powered to detect small differences in outcome.⁵⁰ Additionally, the patients in these studies did not benefit from today's systemic therapies. Another common argument against IMLN irradiation is that an IM local recurrence is quite rare (5%).⁵¹ This argument is also seriously flawed. The location of the IMLN—retro coastal/sternal—is not an area that lends itself to easy palpation, unlike the axilla and supraclavicular regions. Thus, a physical exam alone is unlikely to detect an IMLN recurrence.

The true rate of IMLN metastases is difficult to determine. In lymphoscintigraphy series, IMLN drainage was identified in 9–22% of patients.⁵²⁻⁵⁶ Many of these studies attempted to biopsy the draining lymph node. When successful, 14–24% of the patients were pathologically positive.^{54,55} When one considers the higher rate of nodal positivity seen in pathologic series, the sentinel node biopsy (SNB) technique may not be appropriate for the IMLN chain. This is supported by the studies from Veronesi and colleagues and Yu and associates.^{57,58} Two trials, which are 2 decades and a continent apart, reported very similar rates of IMLN metastases in women undergoing IMLN dissection. In these series, there was a 9–13% risk of pathologically positive IMLNs in women with a node-negative axilla.^{57,58} However, the risk increased to 28–37% in women with a pathologically positive axilla. Jiang and coauthors reported their experience with thorascopic internal mammary lymphatic chain dissection in breast cancer patients with large primaries

and/or clinically positive axillary lymph nodes. The authors found that 50% of these patients had IMLN metastases.⁵⁹ Other factors associated with a positive IMLN include medial and central tumors, LVI, and positive axillary lymph nodes.⁵⁰

Although IMLN metastases are associated with decreased survival, there is now ample evidence that treatment of the IMLNs results in improved outcomes.⁶⁰ Veronesi and colleagues recently published the results of 663 women with primarily inner quadrant breast cancer who underwent lymphoscintigraphy for SNB. The radiation was adjusted to include the IMLNs if they were found to be positive. In their study, there was no difference in OS between patients with positive and negative IMLNs. The authors attribute this lack of difference in survival to the IMLN RT. Secondly, there is an accidental trial reported by Stemmer and associates. In this report, women on a bone marrow transplant trial received PMRT, which included IMLN irradiation via electrons.⁶¹ Halfway through the trial, the authors lost electron capability and consequently discontinued IMLN RT. When the authors reviewed their data, there was a statistically significant improvement in disease-free survival (DFS) and a trend towards improved OS in favor of IMLN irradiation. Thirdly, the 3 modern PMRT trials, all of which irradiated the IMLNs, are the first to show a clear survival benefit with PMRT.^{5,7,22} Finally, in 2007, the EBCTCG presented the result of a meta-analysis of more than 9,000 node-positive women treated with mastectomy, and randomized to radiation or no radiation. In this meta-analysis, which showed a statistically significant survival benefit in women treated with PMRT, the IMLNs were irradiated in 24 of the 25 studied trials.^{14,50} Given the evidence above, one should not automatically discount the importance of IMLN irradiation in women receiving PMRT for node-positive breast cancer.

Radiation Toxicity

Acute Effects

Radiation therapy, although beneficial in improving both local control and survival, is not without social and physical costs. The social costs are lost time from loved ones and livelihood, while the physical costs may include rib, lung, nerve, and soft tissue damage. It is important to note that toxic effects of radiation can be affected by several treatment- and patient-related factors. Treatment factors include type and energy of radiation, area treated, dose, fraction size, immobilization devices, dosimetric plans, and systemic therapy.^{62,63} Patient-related factors associated with increased toxicity include obesity (high body mass index [BMI]) and comorbidities (ie, diabetes, connective tissue diseases, renal failure, smoking, and previous radiation exposure).⁶⁴

Side effects or toxicities can be separated into 2 general categories: early and late. Early or acute toxicities occur during the course of radiation, whereas late toxicities may occur 6 months to several years after radiation. The most common acute side effects from whole breast radiation are fatigue and skin irritation. These side effects, and all others, vary greatly from patient to patient. The fatigue tends to be very mild, such that many women are able to continue working full time during the course of treatment. Skin irritation (radiation dermatitis) is also fairly common. In some reports, as many as 90% of patients will develop some form of radiation dermatitis.⁶⁵

The deep layer of the epidermis contains basal stem cells. These stem cells are responsible for the cells that make up the cornified layer of the epidermis. Radiation damages the stem cells. As a consequence, there is shedding of the cornified layer: dry desquamation. The radiation will also cause capillary dilatation, increased permeability, and an inflammatory response resulting in erythema and edema. There is also hyper-pigmentation from migration of the melanocytes to the surface, epilation, and loss of sweat and sebaceous glands resulting in dry and pruritic skin. With continued loss of the basal cell layer, the dermis will become exposed: moist desquamation. This may progress to frank ulceration. Healing entails re-epithelialization via repopulation of the residual basal cells or migration of basal cells from neighboring areas.^{65,66}

There are a multitude of putative treatments available for acute radiation-induced skin toxicity. However, very few have been proven to be more effective than best supportive care in clinical trials. Putative therapies include washing with mild soap, aloe, barrier films, corticosteroids, anti-microbial creams (silver sulfadiazide), and trolamine. Two therapies have been studied in a prospective fashion and found to be somewhat effective. In a randomized prospective trial, *Calendula officinalis* cream was found to significantly reduce skin toxicity when compared to trolamine.⁶⁷ Trolamine has been shown to be no better than best supportive care. Hyaluronic acid cream, when compared in a randomized prospective trial to placebo, was found to significantly delay the onset of severe skin toxicity.⁶⁶ While ensuring a reduction in skin toxicity is a laudable goal, given the lack of effective agents, one should at minimum provide supportive care including, if possible, pain relief.

Late Effects

Due to their proximity to the chest wall, certain organs/structures may suffer radiation-induced toxicities. One such toxicity is radiation pneumonitis (RP). RP is characterized by interstitial inflammation within the irradiated field, a nonproductive cough, and/or low-grade fever. The risk of developing RP ranges from 1–29% and has been linked to patient and treatment factors such as

age, BMI, radiation dose/volume and treatment fields, and chemotherapy and hormonal therapy.^{64,68-71} The literature supporting these putative predictive factors for RP is mixed. For example, Taghian and colleagues and Burstein and associates reported an increase in the risk of RP with concurrent and sequential taxane chemotherapy.^{72,73} However, others were not able to find a relationship between standard dose chemotherapy and RP in women receiving radiation.^{64,74} There is also some debate as to whether dose-volume histograms metrics can accurately predict the risk of RP. While some researchers have correlated NTCP, V13 (Volume that receives 13 Gy), V20, and V30 with RP, others have found no such correlation.^{64,68,70,71,75} Although there is some debate about predictive factors for RP, one should always minimize the incidental lung exposure. Using modern radiation techniques and standard doses to treat the chest wall and regional nodal groups, the modern risk of symptomatic RP appears to be closer to 1–7%.^{7,64,68} A short course of corticosteroids followed by a slow taper has been used successfully to treat this condition.

Another very rare and unique lung complication is radiation-associated bronchiolitis obliterans organizing pneumonia (BOOP). In the few papers describing this entity, the incidence appears to be 0.5–2%.^{76,77} It is characterized by ground glass opacities/interstitial changes extending beyond the irradiated lung, and appears to be migratory in nature. BOOP associated with radiation is seen most commonly in older patients and those receiving concurrent endocrine therapy. Treatment is typically a prolonged course of corticosteroids, which may last months to years.

Cardiotoxicity

With left PMRT, there is a risk of radiation exposure to the heart. Meta-analyses using studies with outdated radiation techniques have shown an increased rate of cardiac events in those who received radiation compared to those who did not.³ This increase in cardiac events was not obvious until 15 years after therapy. However, today, with modern radiation machines and techniques there is little evidence to suggest a significant increase in cardiac morbidity with radiation. For example, in the 3 modern PMRT trials in which the chest wall, supraclavicular, axillary, and IMLNs were treated, there was no statistically significant difference in cardiac morbidity between those who did or did not receive radiation.^{7,62,78} Yet, as the use of systemic chemotherapy increases, especially with agents known to be cardiotoxic such as anthracyclines and trastuzumab (Herceptin, Genentech), it is necessary to remain vigilant in avoiding and assessing potential radiation-induced cardiac toxicity.

Some institutions use active breathing control or respiratory gating when treating the left breast to decrease

the amount of heart that is irradiated.⁷⁹⁻⁸¹ With active breathing control, the patient is coached to hold their breath when the lung is expanded to 80% of its maximum volume. Radiation is only delivered during the breath hold. Chest expansion with breath hold increases the distance between the heart and the chest wall and therefore lowers the radiation exposure to the heart. Systems using respiratory gating track the breathing cycle with an external fiducial marker. The radiation is gated so that it only activates during the deep inspiration part of the breathing cycle when the heart is furthest from the chest wall.

Lymphedema

Lymphedema, abnormal swelling of the ipsilateral arm as a result of disrupted lymph flow, is perhaps one of the most feared late effects of radiation. The definition of clinically significant lymphedema varies greatly in the literature. Some define lymphedema as a greater than 2 cm circumference difference between the affected and nonaffected arm measured at 10 cm above and below the olecranon. Others define lymphedema as a cumulative difference of greater than 10 cm between the measurements, and still others look for a difference in volume measured by water displacement when the arm is placed in a water bath. In part, as a consequence of a nonuniversally accepted definition, reported rates of lymphedema vary greatly. The highest rates appear to be associated with a full axillary dissection (levels I-III) combined with axillary radiation.^{82,83} Other factors have been associated with an increased risk of lymphedema such as obesity, age, hypertension, infection, radiation fields and dose, number of nodes removed, and number of nodes containing metastatic disease.^{83,84-87} Fortunately, rates appear to have dropped significantly with the advent of SNBs, limited nodal dissection (levels I-II only), and judicious use of modern radiation techniques. In the PMRT randomized trials, where patients had all regional nodal groups irradiated, after an axillary nodal dissection, the incidence of lymphedema was 9–14%.^{7,62} In the BC trial, there was no significant difference with respect to symptomatic lymphedema between the groups that did or did not receive PMRT. Unfortunately, there is no cure for lymphedema. Intervention is motivated by the desire to palliate symptoms and reduce risk of complications. Management of lymphedema includes massage, sequential compression, and compressive garments.⁸⁸ Patients are also instructed to avoid infections, blood draws, or blood pressure screenings in the arm at risk. We recommend that the patient be seen by a lymphedema specialist at the earliest sign of arm swelling.

Second Non-breast Malignancy

Another feared and often-mentioned potential side effect of radiation is the development of a second non-breast malignancy. Approximately 7–8% of women undergoing

adjuvant radiation for breast cancer will develop a second non-breast malignancy. However, when compared to similar patients who did not undergo radiation, there appears to be a very small to insignificant difference in the rate of second non-breast malignancies.^{89,90} While Obedian and colleagues and Woodward and associates found no overall significant difference in the rate of second malignancy between women who did and did not receive radiation for breast cancer, Galper and coworkers reported a 1% absolute increase in second non-breast malignancies associated with radiation.⁹¹

There have been mixed reports with respect to the possible increased risk of lung cancer in women who smoke and receive radiation for breast cancer. Harvey and coauthors reported an increase in lung cancer in women treated with radiation for breast cancer.⁹² Zablotska and Neugut reported a statistically significant increase in lung cancer in women treated with PMRT, but not lumpectomy and radiation. In addition, this increased risk was not evident until 10 years after exposure.⁹³ Obedian and colleagues found no increased risk of new lung primaries in women treated with breast-conserving therapy compared to those treated with mastectomy alone. However, the authors did report a correlation between lung primaries and smoking. The 15-year risk of developing lung cancer after breast-conserving therapy was 0.3%, 4.7%, and 6% for nonsmokers, previous smokers, and current smokers, respectively.⁸⁹ There is a report suggesting an increased risk of AML associated with radiation for breast cancer. However, the authors were not able to show whether this was independent of chemotherapy.⁹⁴

Second Breast Malignancy

Contralateral breast cancer (CBC) is the most common second primary malignancy in women diagnosed with breast cancer.⁹⁵ While it is known that different breast/chest wall radiation treatment techniques may expose the contralateral breast to 0.5–7.1 Gy, the data showing a correlation between CBC risk and radiation are inconclusive. In a review of 134,501 women diagnosed with breast cancer between 1973 and 1996 in the SEER database, Gao and colleagues demonstrated an overall 4.25% incidence of CBC.⁹⁵ On multivariate analysis, there was no correlation between radiation and CBC. However, on subset analysis, the authors report an absolute 1.6% increased risk of CBC at 20 years in women treated with radiation. The results of this study are uncertain, as the information is from a large centralized databank, which lacks treatment details. Some authors have shown a correlation with increased CBC rate and radiation, but only in women younger than 45 years old, whereas others found no correlation in any subset of women.^{89,96} On analysis of EORTC trial 10853, which randomized women after lumpectomy

for ductal carcinoma in situ to radiation or not, there was a small but significant increase in CBC in the irradiated group.⁹⁷ However, in the nearly identical NSABP B-17 trial, there was no significant correlation identified.⁹⁸ Nielsen and coworkers, in review of the Danish Breast Cancer Group PMRT trials, found no significant increase in CBC in women who received radiation.⁹⁹ Therefore, the literature is inconsistent on the correlation between radiation and CBC. Nonetheless, one should use techniques that will minimize radiation exposure to the contralateral breast.

Other late side effects of radiation with standard fractionation include brachial plexopathy (1%), spontaneous rib weakening or fracture (2–3%), decreased shoulder mobility (5%), and grade 2 breast fibrosis (4%).^{68,69}

Conclusion

The main hope is that the reader will leave this review with an understanding of the controversies concerning PMRT. While this review is somewhat broad, it is not exhaustive. Publications are chosen, in the opinion of the author, to best illustrate a point. Therefore, the reader is encouraged to seek out other reviews and primary sources of information to further substantiate their own opinion.

Ten years have passed since the last of the 3 seminal PMRT studies was published. Despite this time and with more than 20 years of patient follow-up, many questions still remain. The way to answer many of these questions is to support clinical trials that address them. Until the results from trials like MA 120 are available, systemic therapy trials can aid in answering these questions by collecting and reporting, not only DFS and OS, but also local therapy and LRR data as well.

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