VOLUME 23 · NUMBER 8 · MARCH 10 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

The Use of Radiotherapy After Mastectomy: A Review of the Literature

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J Clin Oncol 23:1706-1717. © 2005 by American Society of Clinical Oncology

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Submitted August 8, 2004; accepted December 8, 2004.

Author's disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2308-1706/$20.00

DOI: 10.1200/JCO.2005.08.109

INTRODUCTION

Postmastectomy radiotherapy (PMRT) has been shown to significantly reduce the risk of locoregional failure (LRF) and to improve disease-specific survival in high-risk women with early-stage breast cancer.[1-7] Studies have also confirmed its importance in maintaining optimal locoregional control in patients with locally advanced disease.[8,9] Historically, PMRT was delivered before the availability of systemic therapies. However, this review will emphasize the role of PMRT in the presence of adjuvant (or neoadjuvant) systemic therapy.

The content of this review is based upon critical examination of all published randomized trials of mastectomy and systemic therapy with or without radiotherapy (RT), meta-analyses of all PMRT randomized trials, and the published guidelines for PMRT from the National Institutes of Health, the American Society of Therapeutic Radiology and Oncology, the American College of Radiology, the American Society of Clinical Oncology, and Health Canada.[10-14] The outcomes emphasized are LRF, breast cancer–specific survival, overall survival, and non–breast-cancer deaths.

Whenever possible, recommendations were based upon controlled investigations rather than uncontrolled observational studies. The levels of evidence for treatment recommendations were adapted from the criteria proposed by Sackett.[15] Briefly, level I evidence was based on results from large randomized trials with clear outcomes (high power, low risk of error), and/or meta-analyses of well-designed clinical trials; level II was based on small randomized trial results of low power (moderate to high risk of error); level III represented nonrandomized, concurrent cohort comparisons of contemporaneous controls; level IV consisted of reports from nonrandomized comparisons between current patients and historical controls; and level V represented case reports with no historic controls.

RATIONALE FOR PMRT

Virtually every PMRT randomized trial to date has demonstrated a reduction in the risk of LRF with the use of comprehensive RT.[1,2] Prevention of LRF is an important goal in oncology management as, on average, only approximately 50% of locoregional recurrences can be subsequently controlled.[16] Despite the consistent improvements in locoregional control, evidence of a benefit in survival attributed to PMRT has been elusive until recent years.[3-5] Conceptually, for PMRT to improve survival, RT must be able to sterilize residual locoregional disease which, if left untreated, could lead to distant tumor spread. The patients who would potentially benefit are those without micrometastatic disease at presentation or patients with micrometastatic disease effectively treated by systemic therapy. Appropriate patient selection would require identification of factors predicting residual locoregional disease after mastectomy as discussed in Patient Selection for PMRT: Defining Risk.

EFFECT OF SYSTEMIC THERAPY ON LOCOREGIONAL CONTROL

As shown in Table 1, randomized trials have shown inconsistent reductions in the rates of LRF with systemic therapies.[17-31] Almost all agents, particularly hormonal, have resulted in some risk reduction; however, the absolute rates of isolated LRF have remained 15% or higher in most node-positive series, depending upon the baseline estimate of risk (level II evidence).

Recent studies suggest that dose-dense regimens and newer systemic agents do not significantly reduce the risk of LRF beyond that achieved with standard chemotherapy (level II evidence).[32-39] In the Cancer and Leukemia Group B (CALGB) 8541 trial in node-positive breast cancer, randomization between high-, standard-, and low-intensity cyclophosphamide, doxorubicin, and fluorouracil (CAF) resulted in comparable levels of LRF following high- and standard-intensity chemotherapy (ie, 14% and 17% total recurrences, respectively) compared to 27% following low-intensity CAF.[32] Similarly, intensification of cyclophosphamide in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-22 trial did not result in any reduction in the rate of LRF over standard doxorubicin and cyclophosphamide (AC), with 10% risk of LRF with all regimens at 5 years.[33] Retrospective analyses also demonstrate LRF rates of approximately 33% to 40% in the absence of RT despite administration of high-dose chemotherapy with peripheral stem-cell support.[34-36] The impact of taxanes on LRF has not been extensively studied, however, results of locoregional control following AC with or without paclitaxel among patients entered on CALGB 9344 did not demonstrate a significant benefit following paclitaxel in patients treated with mastectomy at 5 years, with rates of isolated locoregional recurrence of 10.8% with AC and 8.8% with AC + paclitaxel without RT ($P = .28$), and 4.3% and 3.5% with RT, respectively ($P = .87$).[37] Results of dose-dense versus conventional AC + paclitaxel (CALGB 9741) showed no difference in risk of LRF by regimen.[39] Collectively, these reports suggest that while systemic therapy can reduce rates of LRF, considerable risk for recurrence persists particularly in high-risk patients.

PMRT: LOCOREGIONAL CONTROL AND IMPROVED SURVIVAL

Randomized trials have consistently shown a highly significant two-thirds reduction in LRF with the addition of PMRT (level I evidence).[6,7] This reduction has been observed despite inclusion of older studies insufficiently powered to demonstrate a benefit and use of RT techniques and targets inadequate by current standards.[1,2,40] Despite the benefit in locoregional control, the effect of PMRT on disease-specific and overall survival has varied. Early analyses suggested decreased survival with PMRT.[41,42] A later report of cause-specific mortality in 4,309 10-year survivors

Table 1. Randomized Trials of Adjuvant Systemic Therapy Versus Observation Following Mastectomy

Trial	Study Years	No. of Patients	Systemic Treatment	Locoregional Failure (%)		Follow-Up (years)
				Control	Systemic Therapy	
Node negative						
West Midlands Oncology Association[17]	1976-1984	543	LMF	19	10	8
Milan[18]	1980-1985	90	CMF	13*	4*	12
IBCSG V[19]	1981-1985	1275	CMF	12	7	5
ECOG/Intergroup[20]	1981-1988	425	CMFP	9	3	4.5
NSABP B-13[21]	1981-1988	760	MF	13	6	8
NSABP B-14[22]	1982-1988	2818	T	7	3	10
Node positive						
NSABP B-05[23]	1972-1974	380	L-PAM	24	14	11
Milan[24]	1973-1975	391	CMF	15	13	19
Guy's/Manchester[25]	1975-1979	370	L-PAM	27	18	*
Guy's/Manchester[26]	1976-1985	391	CMF	44†	18†	8
West Midlands Oncology Association[27]	1976-1984	540	AVCMF	35	31	7
IBCSG III[28]	1978-1981	339	CMFPT	34	21	13
IBCSG IV[28,29]	1978-1981	349	pT	34	16	21
ECOG[30]	1978-1981	265	CMFP CMFPT	13	CMFP 11 CMFPT 9	6
NCCTG[31]	1979-1985	234	CFP CFPT	19	CFP 8 CFPT 9	5

NOTE. In the node-positive trials, the percentage of patients who had ≥ four positive nodes were as follows: 32% in the Milan trial; 28% in the Guy's/Manchester[25]; 41% in Guy's/Manchester[26]; 44% in IBCSG III[28]; 39% in IBCSG IV[28,29]; 48% in ECOG[30]; 40% in NCCTG[31]; and the percentage was not stated in the NSABP B-05 and West Midlands Oncology Association study.

Abbreviations: LMF, chlorambucil, methotrexate, and fluorouracil; CMF, cyclophosphamide, methotrexate, and flurouracil; IBCSG, International Breast Cancer Study Group; ECOG, Eastern Cooperative Oncology Group; CMFP, cyclophosphamide, methotrexate, flurouracil, and prednisone; NSABP, National Surgical Adjuvant Breast and Bowel Project; MF, methotrexate and fluorouracil; T, tamoxifen; L-PAM = L-phenylalanine mustard; AVCMF, doxorubicin, vincristine, cyclophosphamide, methotrexate, and flurouracil; CMFPT, cyclophosphamide, methotrexate, flurouracil, prednisone, and tamoxifen; pT, prednisone and tamoxifen; NCCTG, North Central Cancer Treatment Group; CFPT, cyclophosphamide, flurouracil, prednisone, and tamoxifen.

*Includes breast conservation failures.

†Premenopausal women.

demonstrated that the excess of cardiac deaths associated with RT was offset by a reduction in deaths due to breast cancer, suggesting a benefit from PMRT beyond the established improvement in local control.[43]

The 1995 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated a significant reduction in breast cancer deaths due to RT (odds ratio [OR], 0.94) and also an increased risk of non–breast-cancer deaths (OR, 1.24), resulting in overall mortality rates of 40.3% with RT versus 41.4% without RT (2.6% ± 2.5% reduction in the odds of death).[6] The 2000 EBCTCG overview provided 20-year results of 20,000 women entered into 40 randomized RT trials.[7] Rates of isolated local recurrence were significantly reduced with RT by two thirds (10.4% RT *v* 30.1% control; $2P < .00001$). Breast cancer mortality was significantly reduced by RT ($2P = .0001$) but this benefit was counterbalanced by a significant increase in non–breast-cancer deaths ($2P = .0003$), primarily vascular in origin. In the final analysis, RT resulted in a nonsignificant benefit in overall survival, that is, a 3.9% reduction in the annual death rate ($2P = .06$; level I evidence).

Other meta-analyses have been performed, emphasizing the more clinically relevant PMRT trials.[1,2,40] Van de Steene et al[44] categorized the meta-analysis data by factors that could influence survival and found a significant survival benefit with RT in the more recent trials, as well as trials that utilized standard RT fractionation, and those trials with a favorable baseline crude survival. Whelan et al[45] performed a meta-analysis of the 18 trials in which all patients received systemic therapy. RT significantly reduced the risk of any recurrence (OR, 0.69; $P = .00004$), local recurrence (OR, 0.25; $P < .00001$), and mortality (OR, 0.83; $P = .004$). Even when the two largest trials, Danish Breast Cancer Collaborative Group (DBCCG) 82b and 82c, were excluded,[3,4] PMRT resulted in an 11% reduction in mortality ($P = .17$). Therefore, using specific criteria to select appropriate studies, these analyses demonstrated improvement in overall survival with postoperative RT (level I evidence).

While meta-analyses help to provide evidence to support clinical strategies, large randomized controlled trials are still considered the gold standard when evaluating the relative merits of clinical therapies (level I evidence).[46] The results of the published trials of mastectomy and adjuvant systemic therapy, with or without RT, are presented in Table 2.[3-5,8,9,47-54] Based upon trial size and/or length of follow-up, the DBCCG trials 82b and 82c and the British Columbia Cancer Agency (BCCA) trial provide the greatest level I evidence of a significant benefit of PMRT upon survival.[3-5] In DBCCG 82b, 1,708 premenopausal, high-risk patients with pathologic stage II/III breast cancer were randomly assigned to receive either nine cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) or eight cycles with PMRT.[3] As only 8% of patients in the study were node negative, this trial constitutes a

Table 2. Randomized Trials of Adjuvant Systemic Therapy With/Without Radiotherapy Following Mastectomy

Trial	Study Years	No. of Patients	Systemic Treatment	RT Dose		Locoegional Failure (%)		Overall Survival (%)		Follow-Up (years)
				Gy	No. of Fractions	No RT	RT	No RT	RT	
Mayo Clinic[47]	1973-1980	227	CFP	50	24*	30	10	66	68	5
Dana Farber[48]	1973-1984									
1–3 positive nodes		83	CMF	45	20	5	2	85	77	5
≥ 4 positive nodes		123	CA	45	20	20	6	63	59	5
Helsinki (Klefstrom)[8]	1976-1981	79	VAC±L	45	15	45	10	65	90	5
Glasgow[49]	1976-1982	219	CMF	37.8	15	25	11			5
1-3 positive nodes								54	63	
≥ 4 positive nodes								22	33	
Piedmont[50]	1976-?	76	L-PAM	45-50	30	23	9	48	61	11
		83	CMF	45-50	30	14	5	58	46	11
SECSG[51]	1976-1983	270	CMF	50	25	20	10	35†	45†	10
M. D. Anderson[52]	1978-1980	97	FAC, BCG	Not stated		Not stated		69‡	64‡	3
SSBCG[53]	1978-1985	287	CMF	38-48	Unknown	17	6	Not stated		8
	1978-1985	483	T	38-48	Unknown	18	6	Not stated		8
British Columbia[5]	1978-1986	318	CMF	37.5	16	26	10	37	47	20
Helsinki (Blomqvist)[54]	1981-1984	99	CAFt	45	15	24	7	69	65	7.5
ECOG[9]	1982-1987	312	CAFTH	46	23	24	15	47	46	9
DBCCG 82b[3]	1982-1989	1708	CMF	48-50	25	32	9	45	54	10
DBCCG 82c[4]	1982-1990	1375	T	48-50	25	35	8	36	45	10

Abbreviations: RT, radiotherapy; CFP, cyclophosphamide, flurouracil, and prednisone; CMF, cyclophosphamide, methotrexate, and flurouracil; CA, cyclophosphamide and doxorubicin; VAC±L, vincristine, doxorubicin, cyclophosphamide ± levamisole; L-PAM = L-phenylalanine mustard; SECSG, Southeastern Cancer Study Group; FAC, fluorouracil, doxorubicin, and cyclophosphamide; BCG, Bacillus Calmette Guerin; SSBCG, South Swedish Breast Cancer Group; T, tamoxifen; CAFt, cyclophosphamide, doxorubicin, fluorouracil, and ftorafur; ECOG, Eastern Cooperative Oncology Group; CAFTH, cyclophosphamide, doxorubicin, fluorouracil, tamoxifen, and fluoxymesterone; DBCCG, Danish Breast Cancer Collaborative Group.
*25 Gy/12 fractions delivered followed by 4-week break then additional 25 Gy/12 fractions.
†Extrapolated from survival curves.
‡Disease-free survival.

predominately node-positive study. With median follow-up of 114 months, PMRT significantly reduced LRF (9% *v* 32%; $P < .001$), significantly improved disease-free survival (DFS; 48% *v* 34%; $P < .001$), and significantly improved overall survival (54% *v* 45%; $P < .001$; Fig 1). Multivariate analysis for any type of recurrence or death from any cause revealed a benefit of PMRT in all patients randomly assigned, regardless of tumor size and number of axillary nodes involved. In the recently updated BCCA trial,[5] 318 premenopausal women with node-positive breast cancer were randomly assigned to either 12 months of CMF (later reduced to 6 months) or to CMF with PMRT. At 20-year follow-up, PMRT significantly reduced the crude risk of isolated LRF from 26% to 10% (relative risk [RR] = 0.36; $P = .002$) and improved breast cancer–specific survival (53% *v* 38%; RR = 0.67; $P = .008$) and overall survival (47% *v* 37%; RR = 0.73; $P = .03$; Fig 2). In DBCCG 82c, 1,375 postmenopausal high-risk women with stage II/III disease were randomly assigned to tamoxifen 30 mg for 1 year or tamoxifen with PMRT.[4] With median follow-up of 123 months, PMRT significantly reduced LRF (8% *v* 35%; $P < .001$) and improved DFS (36% *v* 24%; $P < .001$) and survival (45% *v* 36%; $P = .03$; level I evidence; Fig 3).

PATIENT SELECTION FOR PMRT: DEFINING RISK

Clinical and pathologic factors predicting high- (ie, > 20%), moderate- (10% to 20%), and low-risk (< 10%) for LRF are used to categorize the potential locoregional benefit from comprehensive PMRT. Extent of axillary involvement has been shown to predict LRF risk (level II and III evidence). As shown in Table 3, increasing risk of LRF is associated with increasing axillary involvement in the presence of adjuvant systemic therapy.[3-5,48,51,55-57] There is now consistent agreement that patients with ≥ four positive nodes should receive PMRT.[10-14,58,59]

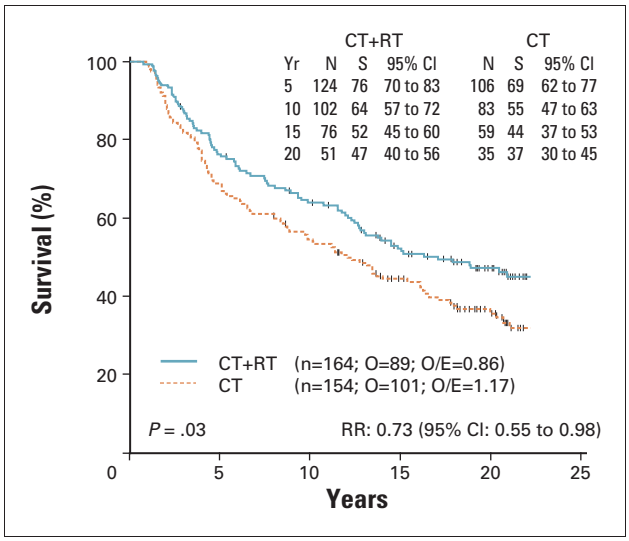

Fig 2. Overall survival in the British Columbia Cancer Agency trial. CT, chemotherapy; RT, radiotherapy; O/E, observed/expected; RR, relative risk. Reprinted with permission from Ragaz J, Olivotto I, Spinelli J, et al: Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 97:116-126, 2005. Copyright 2005 Oxford University Press.

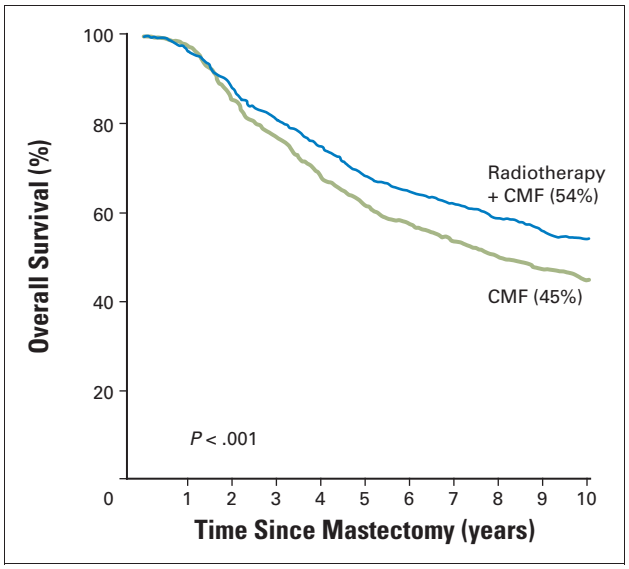

Fig 1. Overall survival in the Danish Breast Cancer Collaborative Group trial 82b. CMF, cyclophosphamide, methotrexate, and fluorouracil. Reprinted with permission from Overgaard M, Hansen PS, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 337:949-955, 1997. Copyright 1997 Massachusetts Medical Society.

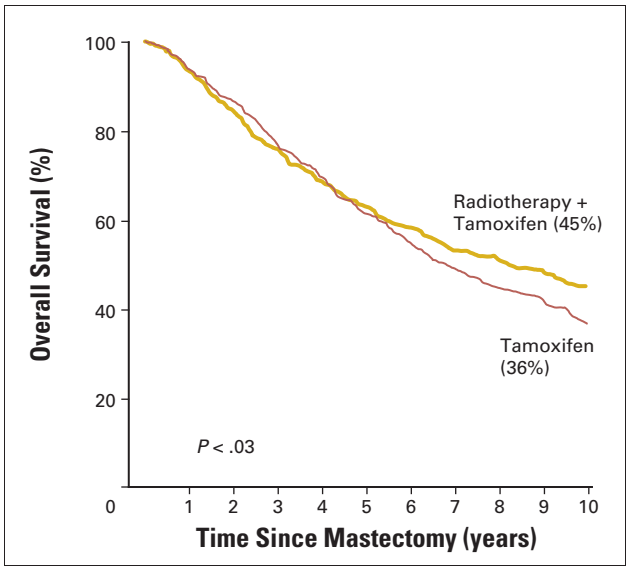

Fig 3. Overall survival in the Danish Breast Cancer Collaborative Group trial 82c. Reprinted with permission from Overgaard M, Jensen M-J, Overgaard J, et al: Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCC 82c randomized trial. Lancet 353:1641-1548, 1999. Copyright 1999 Elsevier.

Table 3. Risk of Locoregional Failure As First Failure by Axillary Involvement Following Mastectomy and Systemic Therapy Without Radiotherapy

Trial	Systemic Treatment	Isolated Locoregional Failure (%)			Follow-Up (years)
		1-3 Positive Nodes	≥ 4 Positive Nodes		
Dana-Farber[48]	CMF	5	—		5
	CAF	—	20		
DBCCG 82b[3]	CMF	30	42		10
DBCCG 82c[4]	T	31	46		10
SECSG[51]	CMF	—	20		10
ECOG[56]	CMF/CMFP/CMFPT/CMFTH	13	29		10
M. D. Anderson[55]	FAC	10	4-9+/21	≥10+/22	10
NSABP[57]	90% with doxorubicin-based chemotherapy	13	4-9+/24	≥10+/32	10
British Columbia[5]	CMF	21(15*)	41(22*)		20

Abbreviations: CMF, cyclophosphamide, methotrexate, and flurouracil; CAF, cyclophosphamide, doxorubicin, and fluorouracil; DBCC, Danish Breast Cancer Collaborative Group; T, tamoxifen; SECSG, Southeastern Cancer Study Group; ECOG, Eastern Cooperative Oncology Group; CMFP, cyclophosphamide, methotrexate, flurouracil, and prednisone; CMFPT, cyclophosphamide, methotrexate, flurouracil, prednisone, and tamoxifen; CMFTH, cyclophosphamide, methotrexate, fluorouracil, tamoxifen, and fluoxymesterone; FAC, fluorouracil, doxorubicin, and cyclophosphamide; NSABP, National Surgical Adjuvant Breast and Bowel Project.
*Crude rates of failure.

The recommendations are less clear in patients with one to three positive nodes. Despite the evidence from the DBCCG and the BCCA studies in support of a survival benefit with PMRT in all node-positive patients, debate remains regarding the applicability of their findings to moderate-risk patients (ie, women with one to three positive nodes). Concerns raised include the incompleteness of the surgical resections, use of older methotexate-based regimens (DBCCG 82b and BCCA trials), use of 1 year only of tamoxifen (DBCCG 82c), and the lack of estrogen receptor data in patient recruitment and data analysis (DBCCG 82c). Other studies, however, suggest comparable rates of LRF with doxorubicin-based and methotrexate-based regimens,[55,56] and preliminary results do not suggest a significant reduction of LRF with the addition of taxanes.[37] The rate of overall LRF in the control patients in the DBCCG trials (approximately 30%) was higher than that observed in other series (less than 20%),[48,55,56,60] and analyses of the combined DBCCG studies demonstrated a 13% rate of axillary failures,[61] higher than the 0% to 3% rate commonly observed with a level I/II dissection.[60,62,63] These high rates of LRF reflect, in part, the inability to identify those patients with only one to three positive nodes, given that in the Danish trials, only a median of seven nodes were removed.[64] Thus, while the relative risk reduction for LRF with PMRT in patients with one to three positive nodes may be similar to that with ≥ four nodes positive,[7] the absolute benefit in women with one to three positive nodes may not warrant its routine use when balanced against the potential for radiation-associated morbidities. Some argue, however, that the benefit in locoregional control from PMRT may underestimate the potential survival gains from treatment, and strongly advocate for its use in moderate-risk patients.[65] At this time, insufficient evidence exists to recommend routine use of PMRT with one to three positive nodes.

In the 2000 EBCTCG overview, women with node-negative disease treated with mastectomy and axillary clearance had the lowest risk of LRF without RT.[7] Despite the highly significant two-thirds reduction in risk of isolated LRF with RT (ie, 9.2% in controls and 2.7% with RT; $2P < .00001$), the risk of any recurrence was not significantly reduced (30.2% control and 28.2% with RT; $2P > .1$; level I evidence).[7] Therefore, PMRT is not routinely recommended in cancers less than 5 cm with negative nodes. Recent analyses of results from the International Breast Cancer Study Group trials I through VII suggest, however, that certain tumor-related factors are associated with increased rates of LRF in node-negative disease.[66] Vascular invasion and tumor size greater than 2 cm in premenopausal women and vascular invasion only in postmenopausal women increased the risk of LRF as first failure to approximately 15% to 20% compared to 8% without these factors. Additional trials of PMRT are needed in node-negative breast cancer.

Tumor size appears to be an independent predictor for LRF in most series, with higher failure rates with T3 lesions compared to T1 and T2 disease (level II evidence).[3,4,55,67,68] Rates of failure for pathologic T3N0 cancers, an uncommon presentation, have been reported between 15% and 60% in the presence of systemic therapy (level V evidence).[53,55,69] More recently, tumor size and extent of axillary involvement have been combined to predict cumulative incidences of LRF.[56]

Invasion of the skin or pectoral fascia have been associated with increased rates of LRF.[3,4,60] While these factors were used for eligibility criteria as high risk in both DBCCG 82b and 82c, outcome results were only reported in 82c, where RT reduced LRF in the presence of deep fascia invasion from 45% to 6%, and 34% to 8% with skin invasion (level II evidence).[4]

The extent of axillary surgery appears to affect rates of LRF.[56,61] Recht et al[56] demonstrated increasing LRF with decreasing number of nodes examined in the Eastern Cooperative Oncology Group trials. Extracapsular extension is associated with increasing rates of LRF attributable

to the correlation with the extent of axillary involvement.[70-74] However, the impact of extracapsular extension upon systemic failure and the potential reduction of that risk by locoregional RT is unclear.[75-78] The effect of close/positive margins on LRF is also not well defined.[79-82] A recent paper suggests that a combination of clinicopathologic factors, in addition to positive margin assessment, is needed to predict rates of approximately 20% LRF.[83] At present, insufficient data are available to recommend PMRT based upon these and other clinicopathologic factors, including patient age, estrogen and progesterone receptor status, HER-2/*neu* status, tumor grade, lymphovascular invasion, and p53 overexpression.[84-90]

CLINICAL TARGETS

The choice of RT fields has generally been based upon patterns of LRF. Most mastectomy series show that more than 50% of LRF occur on the chest wall, with the mastectomy scar at greatest risk for recurrence.[91-93] Therefore, treatment to the chest wall is recommended for all PMRT patients. The second most common site of LRF is the supraclavicular/infraclavicular (axillary apex) region. As many as 33% of LRF occur in this region, with absolute rates of first failure reported in up to 18% of patients, depending upon extent of axillary involvement and tumor size (level IV evidence).[91,94,95] While supraclavicular/axillary apex failures are uncommon in patients with one to three positive axillary nodes, failure rates increase in patients with $\geq$ four positive nodes.[56,90] Therefore, PMRT, including a supraclavicular field, is recommended in patients with $\geq$ four positive axillary nodes. Data are insufficient, however, to recommend a third field in patients with one to three positive nodes based strictly upon patterns of failure. However, the survival gains realized after PMRT in the Danish and British Columbia trials were obtained in patients treated with a supraclavicular field, which supports the routine use of a third field whenever PMRT is delivered. Whether the survival benefit can be attributed to the regional irradiation is unknown. Two current randomized trials of regional RT (European Organisation for Research and Treatment of Cancer [EORTC] 22922 and the National Cancer Institute of Canada Clinical Trials [NCIC GTC] Group MA.20 trial) will address this question.

Patterns of failure data suggest the risk of axillary failure to be 0% to 3% after a complete axillary dissection,[53-55] with increasing axillary failures after inadequate surgery (level III evidence).[56,61,96] As the risk of axillary failure is low in an adequately dissected axilla, and the risk of lymphedema increases with the addition of axillary RT,[97,98] routine full axillary irradiation is strongly discouraged following a level I to III dissection.

Whether to irradiate the internal mammary nodes (IMN) remains unclear. Clinically evident IMN recurrences are uncommon.[91,99,100] No randomized trials to date have demonstrated a survival benefit from IMN treatment, however, subset analyses suggest survival benefits with treatment in certain subgroups.[101-104] The IMN were included in the treated volume in the Danish and British Columbia trials, but as previously noted, whether treatment of these nodes contributed to the improvement in survival is not clear. The EORTC and NCIC CTG MA.20 trials should provide insight into the effect of IMN RT upon survival.

RADIATION-ASSOCIATED COMPLICATIONS

Lymphedema

While a general discussion of potential complications associated with PMRT is beyond the scope of this article, three complications—arm lymphedema, pneumonitis/pulmonary fibrosis, and chronic cardiac toxicity—will be presented. Two factors consistently shown to impact lymphedema risk are extent of axillary surgery and use of axillary RT (level V evidence).[97,98] While each of these factors can separately result in risk less than 10%, the additive risk can be as high as 40% following complete (I to III) axillary dissection and full axillary RT.[97,98] Limitation of the regional fields to include only the supraclavicular region and axillary apex appears to reduce this risk (level V evidence),[74,105] and use of computed tomography planning allows identification of the nodal regions and design of conformal fields that may further reduce arm and shoulder morbidity.[106]

Pneumonitis and Pulmonary Fibrosis

Radiation pneumonitis (RP) has been associated with increasing volume of irradiated lung and chemotherapy use. In a series from the Joint Center of Radiotherapy, RP was observed in 0.2% of patients treated to tangent breast fields alone compared to 1.4% in women treated with nodal RT.[107] Use of chemotherapy increased the incidence of RP to 3.3%, and its effect was further increased to 8.8% with concurrent chemotherapy and RT (level V evidence).[106] Taxane use may also increase this risk.[108,109] Estimates for RP vary by RT technique, which largely reflects differences in the volume of irradiated lung.[110] Following careful RT treatment planning, subjective assessments from DBCCG 82b and 82c did not show an increase in the rates of dyspnea and cough following RT compared with controls (level II evidence).[111] The risk of asymptomatic pulmonary fibrosis, as measured by serial chest radiographs, was, however, increased.[111]

Cardiac Toxicity

Radiation-associated heart disease involves a spectrum of clinical diagnoses including pericarditis, pancarditis, cardiomyopathy, and coronary artery disease, with ischemic heart disease (IHD) of greatest clinical significance.[112]

The EBCTCG demonstrated a significant increase in vascular mortality by RT (death rate ratio, 1.30; level I evidence).[7] Individual trials and retrospective series have yielded conflicting data of the effect of RT upon cardiovascular risk.[113-119] Results from the Stockholm trial demonstrated mortality from IHD was significantly higher in those patients irradiated to the greatest volume of the myocardium (relative hazard, 3.2; $P < .05$; level II evidence).[115] Improvements in RT delivery would be expected to reduce treatment-related morbidity. This was shown in the Danish 82b and 82c trials where similar proportions of RT patients and controls died of IHD after 12 years (RR, 0.84; level II evidence).[120] Pierce et al[110] compared multiple PMRT techniques using normal tissue complication probabilities for IHD and demonstrated significant variation in risk predictions by technique.

Three-dimensional, computed tomography–based treatment planning allows individualized planning and utilization of nonaxial beams to ensure coverage of clinical targets while minimizing critical normal tissue exposure.[110] Examples of advantages using three- versus two-dimensional planning are shown in Figures 4 and 5. As shown in Figure 4A, the 95% isodose line encompasses the chest wall volume using standard (two-dimensional) tangents; however, IMN coverage is compromised. Three-dimensional planning allows incorporation of the IMN in the target volume if desired (Fig 4B), while shaping the field to minimize additional lung RT. Depending upon body habitus and heart position in the thorax, chest wall coverage with standard tangents can include a portion of the heart in the RT field (Fig 5A). Three-dimensional planning can provide field-shaping capabilities to eliminate the heart from the RT field while maintaining chest wall coverage (Fig 5B). Newer strategies such as intensity-modulated radiotherapy (IMRT) may provide greater beam conformality while maximizing dose homogeneity and limiting normal tissue exposure.[121]

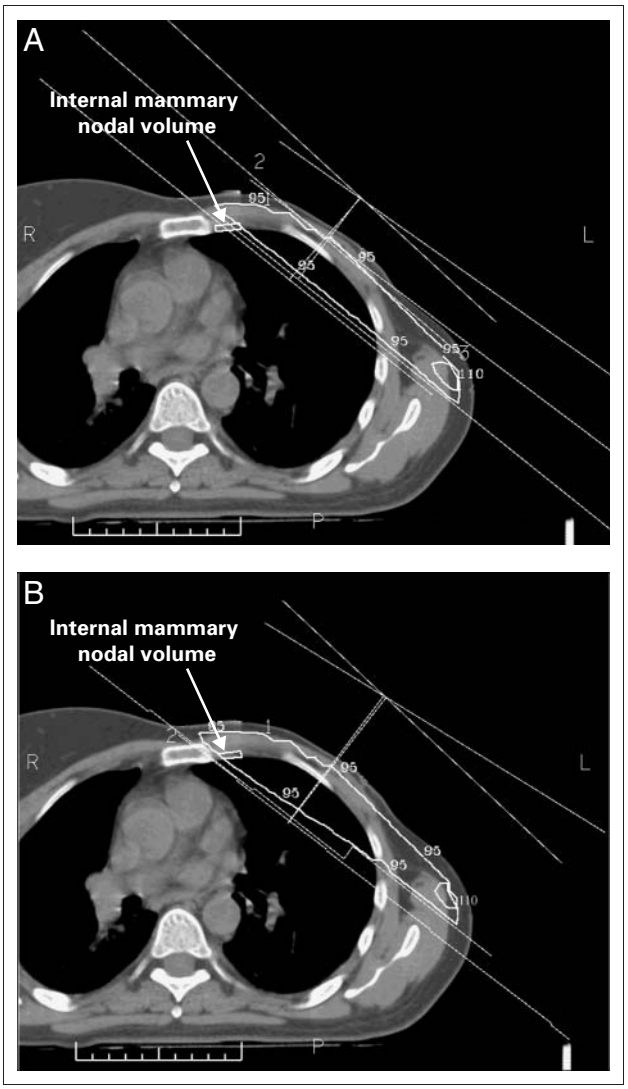

Fig 4. (A) Radiation planning of the upper chest wall using two-dimensional standard tangents; (B) radiation planning of the upper chest wall using three-dimensionally planned tangents.

SEQUENCING SYSTEMIC TREATMENT AND PMRT

No randomized trials have evaluated the optimal sequencing of chemotherapy and PMRT. Information has been extrapolated from breast conservation trials. In a randomized trial of a 12-week course of chemotherapy sequenced before or after RT, no significant differences in time to failure or overall survival were observed by treatment arm (level II evidence).[122] Preliminary results of other sequencing studies also show no difference, but longer follow-up is needed.[123,124] Sequencing options include sequential versus concurrent therapies. Concurrent chemotherapy and RT has been associated with increased complications compared with sequential treatments.[125,126] While strategies have been proposed to decrease the risk of complications with concurrent therapies,[127,128] in general, sequential therapies have been better tolerated. Options for sequential therapies include administration of chemotherapy first, RT first, or a "sandwich" approach where RT is given between cycles of chemotherapy. In a series from Grenada, Spain, rates of LRF were 18%, 10%, and 5% at 10 years with chemotherapy first, RT first, and sandwich approach, respectively, with rates of DFS of 46%, 41%, and 57% and overall survival 47%, 48%, and 57%, respectively ($P = .05$; level III evidence).[129] In both DBCCG 82b and BCCA trials,[3,5] PMRT was delivered between successive cycles of chemotherapy and these trials have shown the greatest survival benefit for PMRT. Whether sequencing affected the outcome is unknown. In the meta-analysis by Whelan et al,[45] a multivariate analysis indicated benefit in mortality when RT was started within 6 months of surgery. However, retrospective studies have not suggested an adverse effect on outcome when longer chemotherapy

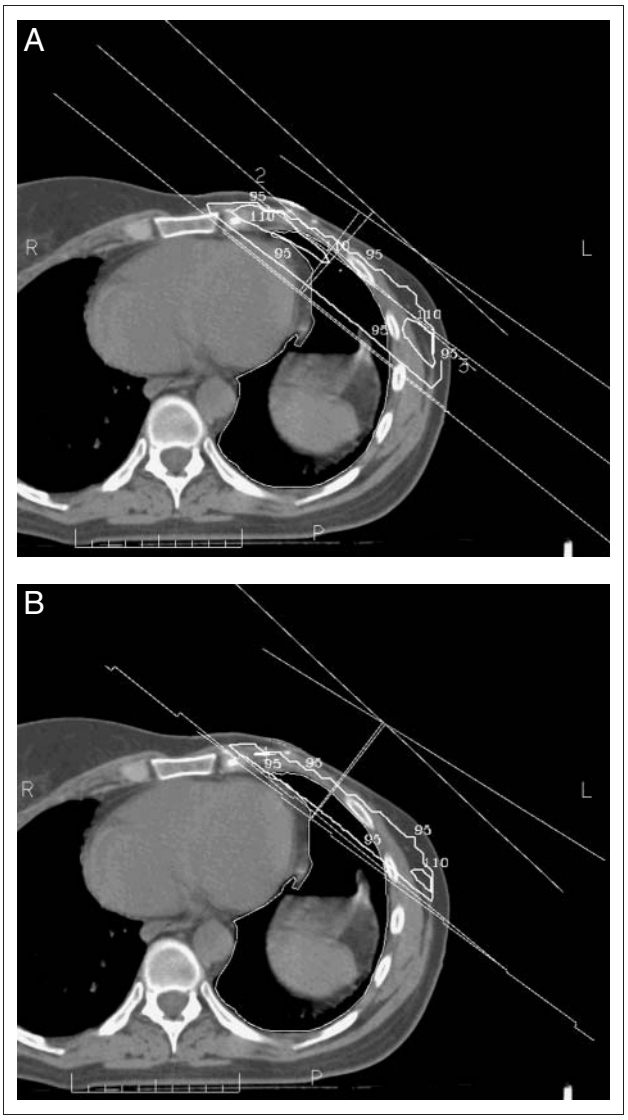

Fig 5. (A) Radiation planning of the lower chest wall using two-dimensional standard tangents; (B) radiation planning of the lower chest wall using three-dimensionally planned tangents, excluding the heart.

schedules were given first.[105] Clearly, the optimal timing of RT has yet to be defined. Of note, dose-dense chemotherapy regimens allow initiation of PMRT earlier than traditional schedules.[39] It will be important to compare rates of LRF following dose-dense schedules. Similarly, the optimal sequencing of hormonal therapies and RT has not been defined. Retrospective series suggest similar rates of in-breast tumor control with tamoxifen administration either after or concurrent with RT[130-133]; however, randomized comparisons are lacking. In the two randomized PMRT studies with tamoxifen,[4,53] tamoxifen was given concurrently with RT, and rates of LRF were significantly reduced with RT (level II evidence). Whether LRF could have been further reduced by sequential administration is unknown.

AREAS OF CONTROVERSY AND FUTURE DIRECTIONS

Whether patients with high-risk, node-negative disease or one to three positive nodes should receive PMRT remains an issue of debate. A randomized trial for PMRT in patients with one to three positive nodes previously open in the United States was closed secondary to inadequate accrual. The Scottish Cancer Trials Breast Group will open a similar trial that will also include high-risk, node-negative women (I. Kunkler, personal communication, January 2005). The primary end point will be overall survival, with secondary end points of disease-free survival, metastasis-free survival, and acute and late morbidity. Information regarding the benefits of regional RT, applicable to both breast conservation and mastectomy patients, will be obtained from the EORTC 22922 and the NCIC CTG MA.20 trials. Accrual to the MA.20 continues, while accrual for EORTC 22922 was completed in January 2004 with 4,004 patients; the first planned analysis is scheduled for approximately 8 years after closure (H. Bartelink, personal communication, August 2004).

Information is needed to define the indications for PMRT following neoadjuvant chemotherapy. Retrospective analyses of patients treated with neoadjuvant chemotherapy suggest that clinical T3 disease, pathologic involvement of $\geq$ four axillary nodes, and no tamoxifen use predict for increased LRF (level III evidence).[134,135] Data from the NSABP-B-18, randomly assigning patients primarily with clinical stage II disease to either adjuvant or neoadjuvant AC, were recently presented.[136] Preliminary results demonstrate no significant difference in the 10-year cumulative incidence of LRF between the two groups. Factors significantly associated with LRF included clinical tumor size and nodal status, and number of pathologically positive nodes (level I evidence). Final analyses of this and other neoadjuvant chemotherapy trials will help to define indications for PMRT.

Another area of needed research is defining the optimal integration of breast reconstruction and PMRT. Increasing reports have demonstrated adverse cosmetic results in irradiated expander-implant reconstructions[137-139]; better results appear to be obtained with autologous procedures (level V evidence).[140,141] However, since not all patients are candidates for autologous reconstruction, information to improve the outcome of expander implants and PMRT, and to further optimize the sequencing of RT and autologous reconstructions is needed. Multidisciplinary input is indicated for optimal care of these patients and prospective studies of adequate power are needed to control for potential confounding clinical variables.

Finally, continued research and implementation of technical advances in RT treatment planning are needed. While three-dimensional treatment planning systems are

readily available for use, practice pattern surveys suggest gradual integration into routine clinical care.[142] Advances in treatment planning such as IMRT and/or active breathing control[121,143] may further improve target coverage while limiting normal tissue exposure. While it is logical that by further reducing treatment-related morbidity, gains in survival will be realized, outcome studies are needed to validate these assumptions.

CONCLUSION

The National Institutes of Health Consensus Panel on Adjuvant Therapy of Operable Breast Cancer and consensus statements from the American Society of Therapeutic Radiology and Oncology, American College of Radiology, American Society of Clinical Oncology, and Health Canada recommend the use of PMRT for patients with ≥ four positive axillary nodes, T3 or T4 lesions, and/or tumor invading the skin or adjacent musculature.[10-14] These groups concur that there is insufficient evidence to recommend PMRT in patients with one to three positive nodes (or high-risk node-negative disease). These patients are strongly encouraged to participate in any available research studies that randomly assign women to the use of PMRT. In the absence of a study, both the potential expected proportional reduction and the absolute reduction in recurrence secondary to PMRT, and the possible improvement in survival, should be discussed with each patient and weighed against the potential for toxicity from treatment.

Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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