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CLINICAL INVESTIGATION **Breast**

INTERNAL MAMMARY NODE IRRADIATION NEITHER DECREASES DISTANT METASTASES NOR IMPROVES SURVIVAL IN STAGE I AND II BREAST CANCER

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Purpose: To compare outcome for ipsilateral breast tumor recurrence (IBTR), or regional node recurrence, initial and subsequent distant metastases, and overall and cause-specific survival in women treated with conservative surgery and radiation based on whether or not radiation was targeted to the internal mammary nodes (IMN).

Methods and Materials: From 1979–1994, 1383 women with Stage I–II breast cancer underwent wide excision, axillary node dissection with ≥10 nodes removed, and radiation. Median follow-up was 6 years; median age was 55 years. A total of 114 women had radiation targeted to the IMN with deep tangents and 1269 did not. Women who received IMN treatment were more often axillary node–positive (40% vs. 25%, $p = 0.002$), had central or inner quadrant tumors (61% vs. 40%, $p = 0.001$), and had T2 tumors (47% vs. 31%, $p = 0.001$). All axillary node–positive women received adjuvant chemotherapy and/or tamoxifen. For axillary node–negative women, 13% of the IMN treatment group received adjuvant systemic therapy compared to 37% of the no treatment group ($p = 0.001$). Radiation was directed to the breast only in 97% of the axillary node–negative women who had IMN treatment and 99% of the no IMN treatment group. For axillary node–positive women, 98% of the IMN-treated group had radiation to the breast and supraclavicular nodes ± a posterior axillary field compared to 77% of the no IMN treatment group ($p = 0.001$). There were no significant differences between the two groups for median age, menopausal status, histology, final surgical margin, estrogen and progesterone receptor status, or the number of positive nodes.

Results: There were no significant differences in the 5- and 10-year cumulative incidence of an IBTR, regional node recurrence, initial or total distant metastases for the two groups. Similarly 5- and 10-year actuarial overall and cause-specific survival were not significantly different. However, subset analysis revealed a statistically significant increase in initial (29% vs. 15% at 10 yr, $p = 0.002$) and total (30% vs. 17% at 10 yr, $p = 0.01$) distant metastases and a significant decrease in cause-specific survival (76% vs. 89% at 10 yr, $p = 0.02$) for postmenopausal women who received IMN treatment. These findings could not be attributed to differences in the use of systemic therapy or the number of positive nodes. Axillary node–positive patients did not experience a significant decrease in initial (36% vs. 22% at 10 yr, $p = 0.21$) or total distant metastases (37% vs. 28% at 10 yr, $p = 0.62$) or a significant improvement in cause-specific survival (72% vs. 76% at 10 yr, $p = 0.76$) with IMN treatment regardless of whether the tumor was lateral or medial/central in location. IMN treatment was not associated with an increase in non–breast cancer deaths during this period of observation.

Conclusions: This retrospective series was unable to identify a significant benefit for IMN irradiation in terms of distant metastases or cause-specific survival for the entire patient population, and in particular, for patients with positive axillary nodes and medially located lesions. The results of the proposed or ongoing prospective randomized trials will further address this controversial issue. **© 2000 Elsevier Science Inc.**

Breast cancer, Internal mammary nodes, Conservative surgery and radiation.

INTRODUCTION

Regional node irradiation was an essential component of many of the randomized trials of postmastectomy radiation. However, two prospective randomized trials comparing conservative surgery and radiation to mastectomy failed to demonstrate a survival benefit with regional node irradiation in axillary node–positive women (in either treatment group) (1–4). These findings, as well as the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B02 trial (5), formed the basis for the omission of regional node irradiation in the NSABP B06 trial and for most of the

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Milan I trial in both axillary node–negative and –positive women. Many radiation oncologists followed the guidelines of the NSABP B06 for patients treated off study and regional node irradiation in patients with an intact breast became a less common practice. Recent studies of conservatively treated women with 0 to 3 positive nodes have also demonstrated that recurrences in the regional nodes (axillary, supraclavicular, or internal mammary nodes [IMN]) are infrequent enough in these women to justify treatment to the entire breast alone (6). Supraclavicular and apical axillary node irradiation has been recommended in patients with 4 or more positive axillary nodes based on their 15 to 20% risk of a supraclavicular recurrence (7–10).

The issue of regional node irradiation has reemerged, primarily in axillary node–positive women, with the publication of three positive prospective randomized trials of postmastectomy radiation (11–13). In particular, it has been suggested that the survival benefit of radiation in the trials could in part be attributed to treatment of the IMN. It has been argued that the benefit which was observed in the absence of an impact on clinical IMN recurrences was due to the elimination of micrometastases in the IMN which could serve as a source of distant metastases. The findings of these trials have prompted the initiation of randomized trials of regional node irradiation in patients with or without an intact breast in Europe, Canada, and the United States. However, the issue remains controversial and the specific benefit of IMN irradiation has been questioned by at least one recent retrospective series (14). In an attempt to address this issue, we have compared outcomes in a group of patients with Stage I and II breast cancer who either did or did not receive radiation targeted to the IMN as part of their breast conservation therapy.

METHODS AND MATERIALS

Between 1979 and 1994, 1383 women with clinical stage I and II (15) breast cancer underwent wide excision, level I–II axillary node dissection with 10 or more nodes examined, and radiation at Fox Chase Cancer Center (782 patients) or the University of Pennsylvania (601 patients). Patients from the University of Pennsylvania were treated and/or followed by one of the authors (B.F.). The median follow-up was 6 years for all patients and 6.5 years for survivors (range 0.1–16.6). The median age was 55 years (range 22–89 years). One-third of the women were premenopausal with 6% perimenopausal and 61% postmenopausal. Sixty-seven percent had clinical T1 tumors ($\leq$2 cm) and 33% had T2 tumors. Mammography alone was the primary method of detection in 31%. The tumor was located in the outer quadrant of the breast in 801 patients (58%), in the central aspect (12 o'clock or 6 o'clock) or periareolar region in 233 patients, and in the inner aspect in 282 patients. Eighty-nine percent had an invasive ductal carcinoma with or without associated ductal carcinoma *in situ*. Six percent of the patients for whom the extent of the intraductal component was assessed had an extensive intraductal component as defined by Schnitt *et al.* (16). The majority of the tumors were estrogen and progesterone receptor positive. Twenty-seven percent had positive axillary nodes with 1–3 positive nodes in 19% and 4 or more positive nodes in 7%. The final resection margin was negative ($>$2 mm) in two-thirds of the patients. Adjuvant systemic therapy was administered to all node-positive patients and 35% of the node-negative patients. Treatment consisted of chemotherapy alone in 307 patients, tamoxifen alone in 296 patients, and a combination of the two in 122 patients. Seventy-nine percent of the patients receiving chemotherapy had CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and 17% had CAF (cyclophosphamide, doxorubicin, 5-fluorouracil). Tamoxifen was prescribed for a minimum of 5 years during this period.

All patients received radiation to the entire breast via tangential fields to a total dose of 46–50 Gy in 1.8 to 2.0 Gy fractions over a period of 4.5 to 5 weeks. Two hundred ninety-six patients received treatment to the supraclavicular nodes with a single anterior field angled 12° with or without a posterior axillary supplement. A dose of 46–50 Gy was delivered at a depth of 3 cm over 4.5 to 5 weeks. Six MV photons were used for the supraclavicular field in all patients and the majority of the tangential fields. Women with large breasts or a separation greater than 21–22 cm were treated with 10, 15, or 18 MV photons with a beam spoiler. The primary site received an additional 14–20 Gy with electrons, external beam, or an iridium-192 implant so that the total dose to this region ranged from 60–66 Gy.

The patients were divided into two groups based on whether the IMN had been targeted with deep tangents. All treatment plans were reviewed and a designation of IMN treatment was made only if the prescription isodose curve in the central axis included a point located 3 cm deep to the skin surface and 3 cm from midline to the ipsilateral side. The dose delivered to this point was a minimum of 46 Gy in 4.5 weeks. None of the patients had their IMN treated with a separate photon or electron beam field or a mixed photon–electron beam field. The decision to treat the IMN was based on individual physician preference. One hundred fourteen patients received treatment to the IMN and 1269 did not. The comparability of the two groups was assessed in terms of the clinical factors of age, menopausal status, primary tumor size, and method of detection; the pathologic factors of histology, presence of an extensive intraductal component, final margin status, pathologic nodal status, estrogen and progesterone receptor status, and the treatment-related factors of reexcision, regions treated with radiation, and median total dose to the primary and the use of adjuvant therapy. The patients were also further divided by the location of the primary as outer or medial (central and inner quadrants). The analyses were initially performed separately for central and inner quadrant tumors; however, no differences were observed between these two groups and they were subsequently combined. Statistical comparisons were performed by the Pearson chi-square statistic or Fish-

Table 1. Comparison of clinical factors

	All pts.			Outer			Inner/Central		
IMN Treatment	Yes	No	*p* Value	Yes	No	*p* Value	Yes	No	*p* Value
No. pts.	114	1269		44	757		70	512	
Clinical tumor size			0.001			0.015			0.007
≤2 cm	60 (53%)	873 (69%)		22 (50%)	513 (68%)		38 (54%)	360 (70%)	
2.1–5 cm	54	396		22	244		32	152	
Median age (yr)	54	55	0.70	53	54	0.58	55	55	0.95
Range	27–85	22–89		22–85	22–87		27–80	24–89	
Menopausal status			0.88			0.80			0.94
Pre	39 (34%)	416 (33%)		16 (36%)	256 (34%)		23 (33%)	160 (31%)	
Post	69	773		26	448		43	325	
Peri	6	80		2	53		4	27	
Method of detection			0.001			0.01			0.001
Mammo only	16 (14%)	409 (32%)		10 (23%)	240 (32%)		6 (9%)	169 (33%)	
Physical examination only	34	239		17	148		17	91	
Both	64	620		17	368		47	252	

er's exact test (17, 18). All reported significant levels are based on two-sided tests.

Results are presented in terms of ipsilateral breast tumor recurrence (IBTR), regional node failure, distant metastases as first site of failure or subsequent to an isolated local–regional failure, cause-specific and overall survival. An IBTR was defined as the first site of failure in the treated breast with or without a regional node failure without simultaneous distant failure. An isolated regional node failure was defined as the first site of failure in the ipsilateral axillary, supraclavicular, or internal mammary nodes without a simultaneous breast or distant failure. Calculations of breast, regional node, or distant failure were made using the methodology of cumulative incidence with comparisons made by using Gray's test (19, 20). Events for cause-specific survival included only deaths from breast cancer. The Kaplan-Meier method (21) was used to estimate survival curves with time beginning at the initiation of radiation. The log rank statistic was used to compare curves (22). A p value of ≤ 0.05 conferred statistical significance.

RESULTS

A comparison of the clinical characteristics is presented in Table 1. Significant differences between the two groups were observed for primary tumor size and method of detection. Women who received IMN treatment had a significantly higher percentage of T2 tumors (47% vs. 31%, $p = 0.001$) and significantly lower rate of detection by mammography alone (14% vs. 32%, $p = 0.001$). In addition, these women more often had medially located tumors (61% vs. 40%, $p = 0.001$). The differences in tumor size and method of detection were observed for all patients regardless of the location of the primary.

Table 2 presents a comparison of the pathologic features. Significant differences were observed only for the pathologic nodal status. Forty-one percent of the IMN-treated women had positive nodes compared to 26% of the women who did not have their IMN targeted. As might be expected, the majority of women with outer quadrant tumors who had IMN treatment had positive nodes (61% vs. 29%, $p = 0.001$). There were no significant differences between the two groups for medial tumors in terms of nodal positivity (27% vs. 20%, $p = 0.21$). This finding reflects the tendency to treat the IMN based on tumor location irrespective of the nodal status for medial lesions. IMN treatment for outer quadrant tumors was reserved primarily for those with positive nodes. For women with positive axillary nodes, there was no significant difference in the percentage of those with 4 or more positive nodes for the two groups, i.e., 26% IMN treatment vs. 27% no IMN treatment.

Table 3 presents a comparison of the treatment-related factors. Patients with medial lesions receiving IMN treatment had a statistically significant lower incidence of reexcision (43% vs. 58%, $p = 0.02$). For all comparisons the IMN-treated group had a lower percentage of negative final margins although the differences were not statistically significant (Table 2). The median total dose to the primary was 64 Gy for the IMN-treated patients compared to 62 Gy for the no treatment group, $p = 0.008$. The higher percentage of close, positive, or unknown margins in this group is responsible for the higher median total dose to the primary. For women with negative axillary nodes, 3% of the IMN-treated group also received radiation to the supraclavicular nodes compared to 1% of the no treatment group, $p = 0.003$. For axillary node–positive women, 98% of the IMN-targeted group received supraclavicular radiation compared to 77% of the no treatment group ($p = 0.001$). Significant differences were also observed for the use of adjuvant systemic therapy. Fifty-two percent of the IMN-treated women received no adjuvant therapy compared to 47% of the no treatment group ($p = 0.01$). This difference primarily reflected a higher percentage of no adjuvant therapy (87% vs. 63%, $p = 0.001$) and a lower percentage of tamoxifen use with or without chemotherapy (7% vs. 25%) in the node-negative IMN treatment group. Similar percent-

Table 2. Comparison of pathologic factors

	All pts.			Outer			Inner/Central		
IMN treatment	Yes	No	*p* Value	Yes	No	*p* Value	Yes	No	*p* Value
No. pts.	114	1269		44	757		70	512	
Histology			0.87			0.77			0.24
Invasive ductal and DCIS	60 (53%)	677 (53%)		25 (57%)	396 (52%)		35 (50%)	281 (55%)	
Invasive ductal	42 (37%)	457 (36%)		14 (32%)	266 (35%)		28 (40%)	191 (37%)	
Invasive lobular ± ductal	5	77		4	56		1	21	
Other	7	58		1	39		6	19	
Extensive intraductal component			0.71			0.35			0.78
Yes	6 (5%)	56 (4%)		3 (7%)	32 (4%)		3 (4%)	24 (5%)	
No	75	828		26	498		49	330	
Unknown	33	385		15	227		18	158	
Final margin			0.13			0.42			0.20
Negative (>2 mm)	57 (50%)	854 (67%)		24 (55%)	505 (67%)		33 (47%)	349 (68%)	
Close (≤2 mm)	10	121		5	70		5	51	
Positive	14	113		6	73		8	40	
Unknown	33	181		9	109		24	72	
Pathologic nodal status			0.002			0.001			0.21
Negative	68 (59%)	948 (75%)		17 (39%)	536 (71%)		51 (73%)	412 (80%)	
Positive	46	321		27	221		19	100	
1–3	34 (30%)	235 (19%)		18 (41%)	160 (21%)		16 (23%)	75 (15%)	
≥4	12 (11%)	86 (7%)		9 (20%)	61 (8%)		3 (4%)	25 (5%)	
Estrogen receptor			0.70			0.85			0.58
Positive	67 (59%)	774 (61%)		25 (57%)	465 (61%)		42 (60%)	309 (60%)	
Negative	22	280		10	173		12	107	
Unknown	25	215		9	119		16	96	
Progesterone receptor			0.99			0.89			0.98
Positive	51 (45%)	648 (51%)		20 (45%)	395 (52%)		31 (44%)	253 (49%)	
Negative	28	357		10	209		18	148	
Unknown	35	264		14	153		21	111	

DCIS = ductal carcinoma *in situ.*

ages of axillary node–positive women received chemotherapy in both groups (78% IMN treatment vs. 74% no IMN treatment).

Table 4 presents patterns of failure. There were no significant differences in the total incidence of IBTR or regional node recurrence for any of the comparisons. There were, however, no IMN recurrences in the treated group compared to 4 in the nontargeted group. All of these 4 recurrences occurred in axillary node–negative patients. Two were outer quadrant lesions and 2 were inner or central. Three occurred simultaneously with distant metastases. There were no IMN recurrences in the 321 axillary node–positive women. Distant metastases as a first site of failure were more frequent in the IMN-treated group irrespective of tumor location. This finding reflects the higher percentage of T2 tumors and axillary node positivity in this group. There were no significant differences in the incidence of distant metastases appearing after an isolated local and/or regional failure. There were more breast cancer deaths in the IMN-treated group, again a reflection of a greater percentage of patients with poorer prognostic features in this group. These differences, however, were not statistically significant. No increase in non–breast cancer deaths was observed in the IMN-targeted group during this period of observation. Non–breast cancer deaths for patients with right-sided lesions occurred in 4% of treated and nontargeted groups. For left-sided lesions non–breast cancer deaths were reported in 2% of the treated group and 4% of the nontargeted group. The incidence of non–breast cancer deaths in premenopausal women was 2% for the treated group and 1% for the nontargeted group. For postmenopausal women the respective percentages were 3% and 5%.

The 5- and 10-year cumulative incidence of an IBTR was 3% and 8% for the IMN-treated group and 4% and 8% for the nontargeted group ($p = 0.43$). For outer quadrant lesions the 5- and 10-year cumulative incidence of an IBTR was 3% and 9% for the treated group and 5% and 9% for the nontargeted group ($p = 0.44$). For central or inner quadrant lesions the 5- and 10-year IBTR were 3% and 8% for the treated group and 3% and 7% for the nontargeted group, $p = 0.60$. There were no significant differences in the cumulative incidence of IBTR for the two groups for comparisons of tumor size, age, the presence or absence of an extensive intraductal component, final resection margin status, or the use of or type of adjuvant therapy. The 5- and 10-year cumulative incidence of an isolated regional node failure was 1% and 1% for both groups ($p = 0.90$) and was similar with comparisons by primary tumor location and pathologic axillary nodal status.

Table 5 presents the 5- and 10-year cumulative incidence

Table 3. Comparison of treatment-related factors

IMN Treatment	All pts.			Outer			Inner/Central		
	Yes	No	*p* Value	Yes	No	*p* Value	Yes	No	*p* Value
No. pts.	114	1269		44	757		70	512	
Reexcision			0.11			0.64			0.02
Yes	57 (50%)	732 (58%)		27 (61%)	437 (58%)		30 (43%)	295 (58%)	
No	57	537		17	320		40	217	
Radiation			0.008			0.41			0.01
Median total dose	64	62		64	62		64	63	
Primary (Gy)									
Path N0	68	948	0.003	17	536	0.80	51	412	0.002
Breast	66 (97%)	945 (99%)		17 (100%)	534 (99%)		49 (96%)	411 (99%)	
Breast, supraclavicular ± PAB	2	3		0	2		2	1	
Path N1	46	321	0.001	27	221	0.008	19	100	0.034
Breast	1	75		0	47		1	28	
Breast, supraclavicular ± PAB	45 (98%)	246 (77%)		27 (100%)	174 (79%)		18 (95%)	72 (72%)	
Adjuvant therapy									
All pts.			0.01			0.14			0.008
None	59 (52%)	599 (47%)		17 (39%)	345 (46%)		42 (60%)	254 (50%)	
Chemo	35	272		16	172		19	100	
Tamoxifen	15	281		6	170		9	111	
Both	5	117		5	70		0	47	
Node-negative			0.001			0.03			0.02
None	59 (87%)	599 (63%)		17 (100%)	345 (64%)		42 (82%)	254 (62%)	
Chemo	4	109		0	61		4	48	
Tamoxifen	5	198		0	110		5	88	
Both	0	42		0	20		0	22	
Node-positive			0.07			0.68			0.03
Chemo	31 (67%)	163 (51%)		16 (59%)	111 (50%)		15 (79%)	52 (52%)	
Tamoxifen	10 (22%)	83 (26%)		6 (22%)	60 (27%)		4 (21%)	23 (23%)	
Both	5 (11%)	75 (23%)		5 (19%)	50 (23%)		0	25 (25%)	

of distant metastases as first site of failure or any time, i.e., total distant metastases. Statistically significant differences were observed for distant metastases as a first site of failure for postmenopausal women irrespective of primary tumor location and for all women greater than 50 years of age and those with the central or inner quadrant tumors. Postmenopausal women and those greater than 50 years of age who did not have their IMN targeted had a statistically significant lower cumulative incidence of initial distant metastases. Similarly, these women also had a statistically signifi-

Table 4. Patterns of failure

IMN Treatment	All pts.			Outer			Inner/Central		
	Yes	No	*p* Value	Yes	No	*p* Value	Yes	No	*p* Value
First sites of failure			0.02			0.38			0.05
Breast	12 (11%)	73 (6%)		5 (11%)	49 (6%)		7 (10%)	24 (5%)	
Breast and reg. nodes	0 (0%)	2 (<1%)		0 (0%)	2 (<1%)		0 (0%)	0 (0%)	
Regional only	1 (<1%)	9 (<1%)		0 (0%)	8 (1%)		1 (1%)	1 (<1%)	
Axilla	0	5		0	5		0	0	
Supraclavicular	1	1		0	1		1	0	
IMN	0	1		0	1		0	1	
Rotter's	0	1		0	1		0	0	
Distant	23 (20%)	153 (12%)		8 (18%)	83 (11%)		15 (21%)	70 (14%)	
Only	23	134		8	72		15	62	
Distant and regional	0	10		0	5		0	4	
Distant + breast ± regional	0	10		0	6		0	4	
Distant after initial local–regional	2 (2%)	21 (2%)	0.71	1 (2%)	15 (2%)	0.60	1 (1%)	6 (1%)	0.59
Deaths from breast cancer	17 (15%)	120 (9%)	0.07	6 (14%)	66 (9%)	0.27	11 (16%)	54 (11%)	0.22
Deaths from other causes	3 (3%)	48 (4%)	0.79	2 (5%)	29 (4%)	0.69	1 (1%)	19 (4%)	0.49

Table 5. 5 and (10) year cumulative incidence distant metastases

	All pts.			Outer			Inner/Central		
IMN Treatment	Yes	No	*p* Value	Yes	No	*p* Value	Yes	No	*p* Value
Initial site of failure ± breast and/or regional									
All pts.	15 (24)	11 (16)	0.08	21 (21)	10 (14)	0.17	12 (25)	12 (18)	0.42
Clinical tumor size									
T1	7 (17)	7 (12)	0.56	11 (11)	6 (11)	0.97	5 (20)	7 (14)	0.67
T2	24 (31)	20 (23)	0.31	31 (31)	18 (21)	0.23	19 (30)	24 (26)	0.96
Age (yr)									
≤35	0 (0)	17 (23)	0.25	0 (−)	19 (24)	0.63	0 (0)	15 (23)	0.33
36–50	9 (13)	15 (18)	0.40	20 (20)	14 (18)	0.74	0 (6)	16 (18)	0.17
>50	19 (30)	8 (14)	0.001	23 (23)	7 (11)	0.07	17 (33)	10 (17)	0.03
Menopausal status									
Pre	6 (14)	15 (19)	0.27	16 (16)	15 (19)	0.88	0 (12)	14 (19)	0.19
Post	22 (29)	10 (15)	0.002	26 (26)	8 (12)	0.03	19 (31)	11 (17)	0.05
Peri	0 (17)	5 (11)	0.97	0 (0)	2 (9)	0.60	0 (25)	12 (12)	0.82
Pathologic nodal status									
Node-negative	11 (16)	9 (14)	0.55	13 (13)	8 (11)	0.77	10 (17)	10 (16)	0.85
No adjuvant therapy	12 (18)	10 (15)	0.47	13 (13)	8 (12)	0.80	12 (20)	12 (19)	0.81
Adjuvant therapy	0 (0)	8 (12)	0.34	—	8 (15)		0 (0)	7 (7)	0.40
Node-positive	21 (36)	17 (22)	0.21	26 (26)	15 (21)	0.44	16 (45)	21 (22)	0.43
Total distant metastases									
All pts.	16 (26)	12 (20)	0.18	21 (25)	11 (19)	0.24	13 (26)	13 (21)	0.54
Clinical tumor size									
T1	9 (22)	8 (15)	0.38	11 (18)	8 (15)	0.65	8 (23)	7 (17)	0.55
T2	24 (31)	21 (28)	0.78	31 (31)	19 (27)	0.52	19 (30)	25 (31)	0.71
Age (yr)									
≤35	0 (20)	21 (27)	0.75	0 (−)	22 (27)	0.14	0 (0)	19 (27)	0.30
36–50	12 (16)	16 (24)	0.40	20 (20)	15 (26)	0.99	6 (11)	16 (21)	0.33
>50	19 (30)	9 (16)	0.009	23 (23)	8 (14)	0.19	17 (33)	11 (20)	0.09
Menopausal status									
Pre	8 (21)	16 (25)	0.39	16 (28)	17 (25)	0.90	4 (17)	15 (23)	0.28
Post	22 (30)	11 (17)	0.01	26 (26)	10 (15)	0.10	19 (31)	12 (19)	0.09
Peri	0 (17)	6 (18)	0.72	0 (0)	2 (14)	0.52	0 (25)	12 (26)	0.78
Pathologic nodal status									
Node-negative	12 (20)	10 (17)	0.45	13 (21)	9 (14)	0.43	12 (19)	11 (19)	0.86
No adjuvant therapy	14 (22)	11 (18)	0.41	13 (21)	9 (15)	0.49	15 (23)	13 (22)	0.85
Adjuvant therapy	0 (0)	8 (13)	0.32	—	9 (16)		0 (0)	7 (7)	0.40
Node-positive	21 (37)	19 (28)	0.62	26 (26)	17 (28)	0.89	16 (45)	21 (27)	0.65

cant lower incidence of total distant metastases. Distant metastases as a first site of failure were lower in premenopausal women and in women ≤50 years of age who received IMN treatment. However, these differences were not statistically significant. For women ≤35 years of age who received IMN treatment there were no initial distant metastases. However, at 10 years the cumulative incidence of total distant metastases was 20% in the treated group and 27% in the nontargeted group ($p = 0.75$). It should be noted that there were only 5 patients in the former group compared to 77 in the latter. IMN treatment was not associated with a statistically significant lower incidence of initial or total distant metastases for axillary node–negative women or, in particular, for node-negative women with inner or central quadrant tumors. For axillary node–positive women, the 10-year cumulative incidence of initial distant metastases was higher in the IMN-treated group ($p > 0.5$) despite a similar percentage of patients in both groups receiving adjuvant chemotherapy. This finding was observed for patients with 1–3 positive nodes as well as those with 4 or more positive nodes. The 10-year cumulative incidence of initial and total distant metastases for women with 1–3 positive nodes was 29% and 29% for the IMN-treated group, and 19% and 24% for the nontargeted group ($p = 0.40$ for initial distant and 0.78 for total distant). For patients with 4 or more positive nodes, the respective numbers for the treated group were 57% and 57% and 28% and 39% for the nontargeted group ($p = 0.31$ for initial distant and 0.62 for total distant).

Table 6 presents actuarial overall and cause-specific survival. Statistically significant differences in cause-specific survival were observed for T1 lesions, women greater than 50 years of age, and postmenopausal women. For each of these categories, IMN treatment was associated with a statistically significant decrease in cause-specific survival. There were no significant differences between the two groups for comparisons of axillary nodal status, irrespective of tumor location. For axillary node–positive women, IMN

Table 6. Kaplan-Meier 5 and (10) year actuarial survival

	All pts.			Outer			Inner/Central		
IMN Treatment	Yes	No	*p* Value	Yes	No	*p* Value	Yes	No	*p* Value
Cause-specific survival									
All pts.	89 (82)	93 (87)	0.38	85 (81)	94 (86)	0.33	91 (83)	91 (87)	0.81
Clinical tumor size									
T1	90 (82)	96 (91)	0.05	88 (80)	96 (90)	0.12	91 (83)	95 (91)	0.31
T2	88 (82)	86 (78)	0.29	75 (75)	89 (78)	0.69	90 (83)	81 (77)	0.28
Age (yr)									
≤35	100 (80)	90 (80)	0.70	100 (−)	86 (77)	0.11	100 (100)	94 (85)	0.22
36–50	90 (90)	90 (83)	0.39	85 (85)	91 (80)	0.96	94 (94)	89 (87)	0.35
>50	88 (80)	94 (90)	0.04	84 (84)	96 (91)	0.30	89 (79)	92 (87)	0.22
Menopausal status									
Pre	94 (90)	91 (81)	0.37	93 (80)	90 (78)	0.94	95 (95)	91 (86)	0.36
Post	85 (76)	93 (89)	0.02	79 (79)	95 (90)	0.12	88 (76)	91 (88)	0.15
Peri	100 (100)	94 (91)	0.46	100 (100)	98 (94)	0.73	100 (100)	84 (84)	0.41
Pathologic nodal status									
Node-negative	92 (88)	94 (90)	0.75	86 (78)	96 (91)	0.09	94 (91)	92 (89)	0.43
No adjuvant therapy	91 (87)	94 (89)	0.66	86 (78)	96 (91)	0.08	92 (90)	91 (87)	0.44
Adjuvant therapy	100 (100)	95 (92)	0.44	—	95 (91)	—	100 (100)	94 (94)	0.46
Node-positive	84 (72)	87 (76)	0.76	84 (84)	89 (76)	0.56	83 (62)	85 (78)	0.38
Overall survival									
All pts.	87 (80)	90 (81)	0.87	81 (77)	91 (81)	0.38	90 (82)	89 (81)	0.60
Clinical tumor size									
T1	86 (78)	93 (86)	0.08	79 (72)	93 (86)	0.03	89 (81)	94 (85)	0.67
T2	88 (82)	84 (72)	0.07	83 (83)	87 (72)	0.35	90 (83)	80 (73)	0.12
Age (yr)									
≤35	100 (80)	88 (79)	0.66	100 (−)	83 (75)	0.14	100 (100)	94 (85)	0.22
36–50	87 (87)	90 (82)	0.55	85 (85)	90 (79)	0.83	89 (89)	89 (86)	0.69
>50	85 (78)	91 (81)	0.53	77 (77)	93 (83)	0.31	89 (79)	89 (77)	0.80
Menopausal status									
Pre	92 (87)	90 (80)	0.48	93 (80)	89 (77)	0.82	91 (91)	91 (85)	0.61
Post	83 (74)	91 (81)	0.34	73 (73)	92 (82)	0.16	88 (76)	89 (78)	0.97
Peri	100 (100)	93 (90)	0.43	100 (100)	98 (94)	0.73	100 (100)	81 (81)	0.36
Pathologic nodal status									
Node-negative	91 (87)	92 (84)	0.50	86 (78)	93 (86)	0.42	92 (90)	90 (82)	0.15
No adjuvant therapy	89 (85)	92 (83)	0.63	86 (78)	94 (86)	0.42	88 (88)	89 (80)	0.19
Adjuvant therapy	100 (100)	93 (86)	0.32	—	93 (85)		100 (100)	93 (88)	0.33
Node-positive	81 (68)	86 (72)	0.67	78 (78)	86 (71)	0.90	83 (62)	84 (77)	0.43

treatment was associated with a nonsignificant decrease in cause-specific survival. For patients with 1–3 positive nodes, the 5- and 10-year actuarial cause-specific survivals were 83% and 78% for the treated group and 90% and 82% for the nontargeted group ($p = 0.60$) (Table 7). For patients with 4 or more positive nodes, the 5- and 10-year actuarial cause-specific survivals were 89% and 38% for the treated group and 81% and 56% for the nontargeted group ($p = 0.84$) (Table 7). For overall survival, a significant difference between the two groups was observed only for T1 outer quadrant tumors, with those receiving IMN treatment having a lower survival. There were no significant differences for axillary node–negative or –positive women. For patients with 1–3 positive nodes, the 5- and 10-year actuarial overall survivals were 80% and 75% for the treated group and 89% and 79% for the nontargeted group ($p = 0.58$) (Table 7). For patients with 4 or more positive nodes, the respective percentages were 81% and 35% and 78% and 51% ($p = 0.98$) (Table 7).

To further evaluate the association between menopausal status, distant metastases, and cause-specific survival, an analysis was performed by nodal status. The 5- and 10-year cumulative incidence of initial distant metastases for axillary node–negative postmenopausal women was 16% and 19% for the IMN-targeted group and 7% and 12% for the nontargeted group ($p = 0.10$). For postmenopausal axillary node–positive women, the corresponding numbers were 32% and 48% for the targeted group and 18% and 22% for the nontargeted group ($p = 0.03$). Total distant metastases were 16% and 19% for the postmenopausal axillary node–negative targeted group compared to 7% and 13% for the nontargeted group ($p = 0.14$). Total distant metastases for the postmenopausal axillary node–positive targeted group were 32% and 49% at 5 and 10 years compared to 21% and 29% for the nontargeted group ($p = 0.14$). The 5- and 10-year actuarial cause-specific survival was 90% and 88% for the postmenopausal axillary node–negative targeted group compared to 95% and 94% for the nontar-

Table 7. 5 and (10) year outcome related to number of positive nodes

	Nodal status			
	1–3		≥4	
	IMN Rx	No Rx	IMN Rx	No Rx
Cumulative incidence DM				
First site	19 (29)	15 (19)	30 (57)	23 (28)
	$p = 0.40$		$p = 0.31$	
Total	19 (29)	16 (24)	30 (57)	25 (39)
	$p = 0.78$		$p = 0.62$	
Actuarial survival				
Overall	80 (75)	89 (79)	81 (35)	78 (51)
	$p = 0.58$		$p = 0.98$	
Cause-specific	83 (78)	90 (82)	89 (38)	81 (56)
	$p = 0.60$		$p = 0.84$	

DM = distant metastases.

geted group ($p = 0.20$). For axillary node–positive postmenopausal women, the 5- and 10-year actuarial cause-specific survivals were 74% and 50% for the targeted group and 87% and 75% for the nontargeted group ($p = 0.11$). For patients with 1–3 positive nodes, the cause-specific survival at 5 and 10 years was 72% and 62% for the targeted group compared to 89% and 81% for the nontargeted group ($p = 0.19$). The corresponding numbers at 5 years for 4 or more node-positive postmenopausal women were 80% in the targeted group and 82% in the nontargeted group ($p = 0.47$). There were not enough patients at risk to report the 10-year interval. Therefore, subset analysis of postmenopausal women reveals in both axillary node–negative and –positive women a higher initial and total cumulative incidence of distant metastases and lower cause-specific survival in women targeted to receive IMN treatment, although none of the differences individually was statistically significant. The findings were observed in women with 1 to 3 positive nodes and those with 4 or more positive nodes.

For axillary node–negative premenopausal women, the 5- and 10-year cumulative incidence of initial and total distant metastases was 0% and 6% and 6% and 19% for the IMN-targeted group and 14% and 18% and 16% and 23% for the nontargeted group ($p = 0.22$ for initial distant and 0.67 for total distant). For axillary node–positive premenopausal women, the 5- and 10-year initial and total distant metastases were 11% and 22% and 11% and 22% for the targeted group and 16% and 22% and 16% and 28% for the nontargeted group ($p = 0.57$ for initial distant and 0.35 for total distant). The 5- and 10-year actuarial cause-specific survival rates were 94% and 84% for the axillary node–negative targeted group and 91% and 82% for the nontargeted group ($p = 0.62$). The corresponding numbers for the axillary node–positive premenopausal targeted group were 95% and 95% and 89% and 79% for the nontargeted group ($p = 0.33$). There were not enough women to do subset analysis by the number of positive nodes. For the two groups, the premenopausal axillary node–positive women had similar rates of initial distant metastases at 10 years, i.e., 22%. However, the nontargeted women had a nonstatistically significant higher incidence of total distant metastases which resulted in a lower 10-year cause-specific survival ($p = 0.33$).

DISCUSSION

The purpose of this study was to compare outcome in terms of ipsilateral breast tumor or regional node recurrence, initial and subsequent distant metastases, and overall and cause-specific survival in women treated with conservative surgery and radiation based on whether or not radiation was targeted to the IMN.

The limitations of the study include its retrospective nature and the fact that the location of the IMN was not assessed by lymphoscintograms or computed tomography (CT)–based treatment planning. Instead, all treatment plans were reviewed and the designation of IMN irradiation was made only if an arbitrary point 3 cm deep to the skin surface at the midsternum and 3 cm from midline to the ipsilateral side was included in the prescription isodose curve. These patients were treated with deep tangents with the medial tangent entering 3 cm or more from midline to the contralateral side. None of the patients had separate IMN fields using electrons, photons, or a mixed beam.

Recht *et al.* (23) estimated from lymphoscintigrams that 83% of the IMN would be included in the tangential fields with the medial tangent entering 3 cm across midline in patients with an intact breast. Bentel *et al.* (24) with CT-based treatment planning in 111 women with an intact breast identified 81% of the patients as having the IMN at a depth of ≤3 cm from the skin surface, and 90% were within 3 cm of midline laterally. The location of the IMN was approximated by identifying the location of the internal mammary vessels. The depth of the IMN correlated with the anterior–posterior (A-P) diameter of the patient. Seven of the 8 patients whose A-P diameter was greater than 24 cm had their IMN located at a depth of >3 cm, compared to 13 of the 103 patients whose A-P diameter was ≤24 cm.

Extrapolating from this data, it can be estimated that at least 80% of our patient population designated as IMN treatment had their IMN treated to a minimum of 46 Gy.

It should be noted that similar problems exist with the two prospective randomized trials of postmastectomy radiation whose survival benefit has been in part attributed to IMN irradiation (11, 12). Neither used lymphoscintigrams or CT-based treatment planning to identify the location of the IMN. In the Danish trial, the depth of the IMN was arbitrarily selected as the depth of the chest wall on ultrasound plus 5 mm (11, 25). In the British Columbia trial, a direct anterior photon beam field was used to treat the IMN and the dose was prescribed at a depth of 3 cm (12). This technique may also have underdosed the deeper nodes. The width of the photon beam was not stated and it is possible that some of the patients with very laterally located IMN would have received inadequate treatment or no treatment to this region. With deep tangents, the coverage of the IMN is influenced primarily by their depth and not their lateral location.

It could also be argued that some of the patients who were designated as not having their IMN treated actually did. Recht *et al.* (23) reported that a medial tangent entrance point 1 cm to the contralateral side would treat 48% of the IMN. Bentel *et al.* (24) reported that 26% of their CT-planned patients had IMN within 2 cm of the skin surface. Therefore, some patients with shallow tangents may have had their IMN inadvertently treated.

Being retrospective, this study reflects the previously recommended guidelines for the treatment of the IMN in that patients whose IMN were targeted had a significantly higher percentage of T2 tumors, tumors detected as a palpable mass, medially located lesions, and tumors with positive axillary nodes.

This study failed to identify significant differences between the two groups for the 5- or 10-year cumulative incidence of an IBTR or regional node recurrence. However, there were 4 internal mammary node recurrences, all in axillary node–negative women who did not receive treatment to this region. Three of the four were associated with simultaneous distant metastases. In contrast, Obedian and Haffty (14) reported a significantly lower breast relapse-free survival in patients who received treatment to the IMN. They attributed this difference to less attention to surgical margins and the diminished use of systemic therapy in the IMN-treated patients. In the present series, there were no significant differences in the percentage of patients with negative margins between the two groups although fewer IMN-treated patients had negative margins (50% vs. 67%). We also had significantly fewer IMN-treated patients receiving systemic therapy (48% vs. 53%, $p = 0.01$), although this finding was primarily limited to the axillary node–negative women.

Initial distant metastases were more frequent in the IMN-treated patients, reflecting their larger primary tumor size and greater percentage of nodal positivity. However, when evaluated by pathologic nodal status and the use of adjuvant systemic therapy, there were no significant differences in initial distant metastases for axillary node–negative women who did or did not receive systemic therapy or for axillary node–positive women all of whom received systemic therapy. There were also no significant differences when comparing patients with 1 to 3 positive nodes or those with 4 or more. Obedian and Haffty (14) also reported no significant differences in the 10-year distant metastasis–free survival when comparing patients with an intact breast who received treatment to the IMN with those who did not. An unexpected finding was the statistically significant increase in initial distant metastases in postmenopausal women who received IMN treatment. This finding was observed for all patients and for those with medial or centrally located tumors. The difference was also statistically significant in the axillary node–positive patients but not in those with negative nodes. This finding could not be explained by differences in the use or type of systemic therapy in these women or the number of positive nodes.

There were no significant differences in the cumulative incidence of total distant metastases for the two groups, except for the postmenopausal women and those greater than 50 years of age. Again the IMN-treated group had a higher cumulative incidence than the nontreated group, although the differences were accounted for by more initial distant metastases. The cumulative incidence of subsequent distant metastases, i.e., total minus initial, was similar for the two groups.

There were no significant differences in the 5- and 10-year actuarial cause-specific survival except for T1 tumors in postmenopausal women and women >50 years of age. For each of these subsets IMN treatment was associated with a statistically significant lower cause-specific survival. For the postmenopausal women, there were no statistically significant differences when comparing axillary node–negative or –positive patients. However, the numerical differences were greatest for the node-positive women (10-year cause-specific survival 50% IMN treatment vs. 75% no IMN treatment, $p = 0.11$).

There were no significant differences for overall survival except for T1 outer quadrant tumors. Patients in this group who received IMN treatment had a statistically significant lower overall survival (72% vs. 86%, $p = 0.03$). We did not observe an increase in non–breast cancer deaths over the period of the study in the IMN-treated group for premenopausal or postmenopausal women or right- or left-sided tumors.

We have not identified a benefit in terms of initial or subsequent distant metastases or cause-specific survival for IMN treatment as given in this patient population. In particular, we found no advantage to such treatment for outer quadrant tumors, inner or central lesions, axillary node–negative or axillary node–positive patients.

Two prospective randomized trials comparing conservative surgery and radiation to mastectomy reported no significant survival advantage to regional node irradiation which included the IMN (1–3). Three prospective random-

ized trials have evaluated the role of regional node irradiation without the confounding effect of chest wall irradiation in postmastectomy patients (5, 26, 27). None of these trials reported a significant survival benefit with regional node irradiation (5, 26, 27). However, it has been suggested that certain subsets of patients may have a greater benefit from IMN treatment. These subsets include axillary node–positive patients and in particular, those with medial or centrally located tumors (26, 28, 29). Two recent series have identified medial quadrant location as an adverse prognostic factor (30, 31). Zucali *et al.* (31) reported a 30% increase in distant metastases and a 20% increase in mortality for 777 patients with a medial or centrally located tumor treated with quadrantectomy, axillary dissection, and radiation with or without CMF when compared to 1619 women with a lateral tumor. The authors suggested that IMN irradiation may be beneficial in these women. Lohrisch *et al.* (30) reported a statistically significant decrease in 5-year systemic disease-free survival and cause-specific survival for 811 women with medial tumors treated with conservative surgery ± radiation or mastectomy and systemic therapy when compared to 2285 lateral tumors. Fifty-six percent were axillary node–positive. There were no significant differences for the women who did not receive systemic therapy, 96% of whom were node-negative. The authors recommended IMN treatment to improve the prognosis in patients with medial lesions.

Several prospective randomized trials have reported a benefit with treatment of the IMN in patients with medial tumors and positive axillary nodes. In the Oslo II trial postmastectomy patients with positive nodes and medial lesions had a 20% improvement in overall survival at 10 years with regional node irradiation following radical mastectomy (26). However, at 15 years patients receiving radiation had a decreased survival. In a randomized trial of radical mastectomy versus extended radical mastectomy, 5- and 10-year survival was significantly improved for central or medial lesions with dissection of the IMN but only when performed by one surgeon (32). The International Cooperative Trial reported a statistically significant improvement in 5-year survival for the extended radical mastectomy for axillary node–positive women with medial T1 or T2 tumors (33). In separate reports of patients entered by the cancer centers at Milan and Villejuif a statistically significant survival advantage for the extended radical mastectomy for medial tumors with positive axillary nodes was reported only by the Villejuif and not Milan (34, 35). The Stockholm trial reported a nonsignificant improvement in 10-year survival with postmastectomy radiation which included the IMN in patients with medial tumors and positive axillary nodes (36, 37). In a retrospective series reported by Arriagada *et al.* (29) treatment of the IMN by surgery, radiation, or a combination of the two resulted in a significant decrease in distant metastases and an improvement in overall survival at 10, 15, and 20 years in patients with medial tumors and positive nodes. In the present study, axillary node–positive women with medially located tumors receiving adjuvant systemic therapy did not have an improvement in distant metastases, cause-specific or overall survival with IMN irradiation. Obedian and Haffty also reported no significant benefit with IMN irradiation in patients with positive nodes or medial lesions in their retrospective series (14).

Our finding of an adverse impact on distant metastases and cause-specific survival in postmenopausal women with IMN irradiation was unexpected. The association was most evident in axillary node–positive women and could not be explained by differences in systemic therapy or the number of positive nodes. We did not observe an increase in non–breast cancer deaths in these women unlike prior studies (38–42), although our median follow-up in survivors was only 6.5 years. Our results are similar to those of Nixon *et al.* and Rutqvist *et al.* (43, 44) in this regard. The Danish randomized trial of postmastectomy radiation in postmenopausal women receiving tamoxifen reported a significant benefit in terms of survival and local–regional recurrence with radiation which included the IMN (13). The specific contribution of treatment of the IMN to these favorable results cannot be discerned.

In summary, this retrospective study provides additional information regarding the potential benefit (or lack thereof) of IMN irradiation in the conservative management of Stage I and II breast cancer. The findings do not support this aspect of treatment and confirm those of one retrospective series and two prospective randomized trials. Further evidence will be forthcoming from the European Organization for Research and Treatment of Cancer (EORTC) randomized trial. At the present time targeted IMN irradiation is not a component of our treatment for Stage I and II breast cancer.

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