

Benefit of Internal Mammary Lymph Nodes Irradiation in Patients with Breast Cancer

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Abstract

Purpose: To evaluate the contribution of internal mammary nodal radiation to the benefit of postoperative radiotherapy in breast cancer patients. The impact on the overall survival (OS), the locoregional relapse-free survival (LRRFS) and distant metastasis-free survival (DMFS) is the endpoint to evaluate the benefit.

Patients and Methods: Between January 2000 and December 2005, breast cancer patients who were treated by either wide local excision or mastectomy followed by radiation therapy to the intact breast or chest wall and regional nodes were divided into two groups; group A including patients treated without targeting the internal mammary chain (IMC) and group B including those treated with a separate field targeting the IMC. The two groups (100 patients in each) were compared with respect to demographic, staging, pathologic, treatment, and outcome parameters. The relevant data were obtained and retrospectively reviewed from the medical records.

Results: Baseline patient and tumor characteristics were balanced between both groups with the exception of age and T-stage. The mean age of group A patients was 50.28 ± 9.887 years compared with 54.48 ± 11.661 years for group B patients ($P=0.018$) and T3-T4 tumors were more likely to be encountered in group B patients (68%) compared with (38%) in group A patients ($P=0.012$). There were no significant difference between both groups at 5 years with respect to the OS (51.5% for group A vs. 57.1% for group B, $P=0.341$), the LRRFS (48.6% for group A vs. 51.9% for group B, $P=0.268$) and the DMFS (46.9% for group A vs. 44.3% for group B, $P=0.836$). Subgroup analysis showed that the benefit of IMC irradiation was limited to patients with 4 or more positive axillary lymph nodes (N2-N3) as evidenced only by better LRRFS (40.2% for no IMC vs. 57.3% for IMC, $P=0.049$). Furthermore, there was a trend toward a better OS in N2-N3 patients who received a separate IMC field but it did not reach the statistical significance (39.8% for no IMC vs. 57.3% for IMC, $P=0.053$).

Conclusion: Postoperative irradiation of IMC with separate field has no benefit with respect to survival parameters in breast cancer patients. It may be considered for patients with N2-N3 stage for better locoregional control.

Introduction

Lymphatic drainage to the internal mammary chain (IMC) of lymph nodes, located in the upper parasternal intercostal spaces, has been observed from all breast

quadrants (1). Because natural lymphatic drainage pathways represent potential routes for locoregional breast cancer spread, the IMC, like the axilla, has long been considered a potential target for treatment in patients with breast cancer. Early studies indicated that IMC involvement, although less frequent than axillary involvement, was not uncommon and did correlate with prognosis in breast cancer patients (2-4). For example, the 10-year disease-free survival rate in an Italian series was 73% when both the IMC and the axilla were negative, 47% when the IMC was negative but the axilla positive, 52% when the IMC was positive but the axilla negative, and 25% when both the IMC and the axilla were positive (5).

The utility of treatment directed specifically to the IMC has been, and continues to be the subject of considerable controversy, particularly in an era when effective systemic chemotherapy and hormonal therapy may be able to treat micrometastatic disease in the IMC and obviate the need for additional treatment (6-7). Studies using sentinel node mapping techniques have raised the possibility that the incidence of IMC involvement may be lower today than was reported in early studies, which generally included patients with more advanced disease than those who present in the modern era of mammographic screening and enhanced public awareness (8, 9).

In theory, treatment of the IMC may be important because occult residual disease in this region may serve as a reservoir from which distant metastases may be seeded. Yet the evidence regarding any actual benefit from treatment directed specifically toward the IMC is unclear. Particular concerns have been raised regarding radiotherapy (RT) for the IMC because of its proximity to vital normal structures, including the heart and lungs specifically if combined with chemotherapeutic agents employing adriamycin or taxol-based regimens with or without dose intensification (10,11). Results from randomized trials testing the value of postmastectomy irradiation and a meta-analysis of 78 randomized trials have provided high levels of evidence that local-regional tumor control is associated with long-term survival improvements. This benefit was limited to trials that used systemic therapy, which was not routinely administered in the earlier surgical studies, although the contribution from IMN treatment is unclear (12).

The purpose of the current study is to evaluate the contribution of internal mammary nodal radiation (IMNR) to the benefit of postoperative radiotherapy in breast cancer patients. The impact on the overall survival, the local recurrence and distant metastasis-free survival is the endpoint to evaluate the benefit.

Patients and Methods

The current retrospective study included all patients with histologically proven invasive breast cancer who were treated at Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 2000 to December 2005. Eligible patients included those who were treated by either wide local excision with or without axillary nodal dissection or mastectomy followed by radiation therapy to the intact breast or chest wall and regional nodes. The relevant data were obtained and retrospectively reviewed from the medical records. All patients' data including demographic, staging, pathologic, treatment, and outcome parameters were analyzed.

For this analysis, the patients were divided into two groups: those treated without targeting the IMC (group A), and those treated with separate field targeting the IMC (group B). The two groups of patients were compared with respect to age, menopausal status, type of surgery, T-stage, number of axillary nodes involved, tumor grade, location of the tumor (right vs. left breast and upper outer quadrant vs. lower outer quadrant vs. upper inner quadrant vs. lower inner quadrant vs. central lesions), ER/PR status and use of adjuvant systemic therapy (chemotherapy and/or hormonal therapy).

Patients were treated with tangential fields to intact breast or chest wall (dose prescribed was 5040 cGy with 1600-2000 cGy boost to tumor bed) with or without supraclavicular and/or IMC fields. The isocenter of supraclavicular field was set at the match line to the tangential fields half blocked at the central axis to avoid divergence into the tangential field. The medial border was set at the patient's midline and angled 15 degrees off the spinal cord. The dose prescribed to this field was 5040 cGy and specified to a depth of 3 cm. The IMC field was generally 5-6cm wide, typically set at or 1 cm across midline to the contralateral breast, and 5 cm toward the ipsilateral side. The field was treated en face with mixed photons and electrons (usually 6 MV or Cobalt 60 photons with 12 MeV electrons). The dose prescribed to the IMC field was 4,600 cGy specified to a depth of 3 cm. In patients treated without a separate IMN field, the medial border of the tangential fields was typically placed at the patient's midline.

Node-positive patients received adjuvant chemotherapy and the regimen employed was anthracycline-based therapy (FAC or FEC) in the majority of patients and to a minor extent CMF regimen. Taxane-based therapy was uncommonly employed as adjuvant chemotherapy for high-risk patients during the study period. Premenopausal and most of postmenopausal patients with hormone-receptor positive tumors received 5 years of adjuvant tamoxifen. aromatase inhibitors (AI) was uncommonly employed (either alone or sequential with tamoxifen) for high-risk postmenopausal patients.

Dates of local recurrence, nodal recurrence, and distant metastases, as well as dates of death and dates last seen alive, were all documented. From this information, overall survival (OS), locoregional relapse-free survival (LRRFS), and distant metastasis-free survival (DMFS) rates were calculated. Survival rates were calculated from the date of breast cancer diagnosis to the date last seen, or to the date of death, whichever came earlier.

Statistical analysis: Data were statistically described in terms of mean \pm standard deviation (\pm SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Survival analysis was done for the different

outcome measures using Kaplan Maier statistics calculating the mean and median survival time for each group with their 95%CI and the corresponding survival graphs. *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

The current retrospective analysis included 100 patients who were treated without targeting the IMC (group A) and 100 patients treated with a separate field targeting the IMC (group B). The median follow-up period for group A was 70 months (range 33 - 108 months) compared with 97 months (range 61 - 132 months) for group B so; there was a longer follow-up of patients treated with a separate field targeting the IMC. There were no statistically significant differences in baseline characteristics between both groups with respect to menopausal status, type of surgery, N-stage, tumor grade, location of the tumor, ER/PR status, or use of adjuvant chemotherapy or hormonal therapy. (**Table 1**)

However, there was a statistically significant difference with respect to age and T-stage. The mean age of patients who received no IMNR was 50.28 ± 9.887 years compared with 54.48 ± 11.661 years for patients received IMNR, ($P=0.018$). T3-T4 tumors were more likely to be encountered in group B patients (68%) compared with (38%) in group A patients, ($P=0.012$). This finding reflected the treatment policy during earlier years of the study that irradiation of the IMC with a separate field in patients is indicated in patients with advanced T-stage (T3-T4) and to omit IMC field in early T-stage tumors.

Table 1: Patient and tumor characteristics of both groups _

	Group A (No IMNR, n=100) N0. (%)	Group B (IMNR, n=100) N0. (%)	P.value
Age:(years)			
< 35	0	0	
36 - 50	56	42	
> 50	44	58	
Mean \pm SD	50.28 ± 9.887	54.48 ± 11.661	0.018
- Median (range)	48.5(38-64)	51.5(36-61)	
Menop. status:			
Premenop.	42 (42%)	34 (34%)	0.537
Postmenop.	58 (58%)	66 (66%)	
Pathology:			
IDC	94 (94%)	98 (98%)	0.362
ILC	6 (6%)	2 (2%)	
Grade:			
I	0 (0%)	0 (0%)	1.0
II	98 (98%)	96 (96%)	
III	2 (2%)	4 (4%)	
Surgery:			
BCS	12 (12%)	6 (6%)	0.487
MRM	88 (88%)	94 (94%)	

Site:			
Rt.	38 (38%)	38 (38%)	0.843
Lt.	62 (62%)	60 (60%)	
Bilat.	0 (0%)	2 (2%)	
Quadrant:			
Central	4 (4%)	0 (0%)	0.135
UOQ	50 (50%)	54 (54%)	
LOQ	26 (26%)	38 (38%)	
UIQ	14 (14%)	8 (8%)	
LIQ	6 (6%)	0 (0%)	
T-stage:			
T1	16 (16%)	6 (6%)	0.012
T2	46 (46%)	26 (26%)	
T3	34 (34%)	50 (50%)	
T4	4 (4%)	18 (18%)	
N-stage:			
0	16 (16%)	2 (2%)	0.134
1	22 (22%)	22 (22%)	
2	40 (40%)	52 (52%)	
3	22 (22%)	24 (24%)	
ER:			
Positive	68 (68%)	70 (70%)	0.757
Negative	32 (32%)	30 (30%)	
PR:			
Positive	58 (58%)	70 (70%)	0.442
Negative	42 (42%)	30 (30%)	
Chemotherapy:			
Yes	94 (94%)	100 (100%)	0.121
No	6 (6%)	0 (0%)	
Hormone therapy:			
Yes	68 (68%)	70 (70%)	0.757
No	32 (32%)	30 (30%)	

Tangential fields alone to intact breast or chest wall without a separate supraclavicular separate were used to treat 28 patients (28%) in group A. However, all patients (100%) in group B were treated by tangential fields with separate supraclavicular and IMC fields. The majority (95%) of node-positive patients included in the study were treated with a separate supraclavicular or supraclavicular/axillary field. The median dose delivered to the IMC field was 4,600 cGy (range 4500 - 5000 cGy).

There were no significant difference between both groups at 5 years with respect to the OS (51.5% for group A vs. 57.1% for group B, $P=0.341$), the LRRFS (48.6% for group A vs. 51.9% for group B, $P=0.268$) and the DMFS (46.9% for group A vs. 44.3% for group B, $P=0.836$) (Fig.1-3). Thus, internal mammary nodal radiation had no benefit or impact on survival parameters. Subgroup analyses were done to determine if there was an advantage to IMNR in any subgroup likely to derive a benefit from such treatment. The analyses were performed evaluating patients by T-stage (T1-T2 Vs T3-T4, number of positive nodes (N1 Vs N2-N3) and location of tumor (medial & central Vs lateral lesions and right Vs left breast). It revealed that the benefit of IMC irradiation was limited to patients with 4 or more positive axillary lymph nodes (N2-N3) as evidenced only by better LRRFS (40.2% for no IMC vs. 57.3% for IMC, $P=0.049$) (Fig. 4). Furthermore, there was a trend toward a better OS in N2-N3 patients who received a separate IMC field but it did not reach the statistical significance (39.8% for no IMC vs. 57.3% for IMC, $P=0.053$).

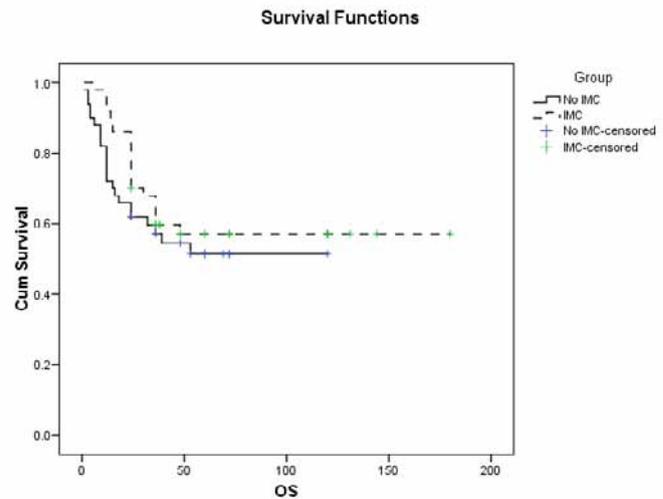


Fig 1: Kaplan-Maier survival curve of overall survival in both groups ($P=0.341$)

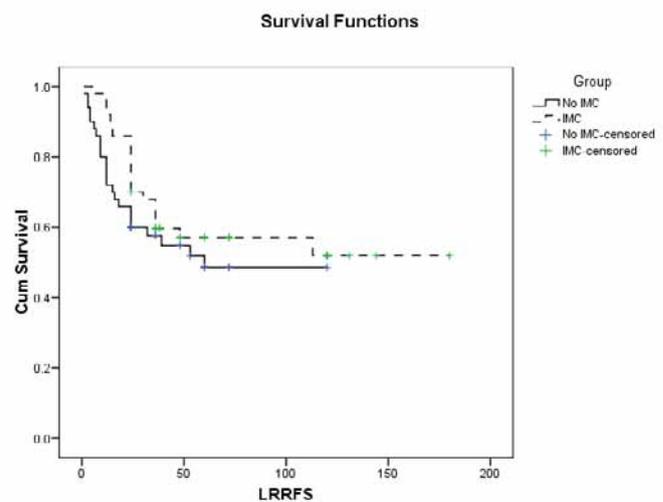


Fig 2: Kaplan-Maier survival curve of locoregional relapse-free survival in both groups ($P=0.268$)

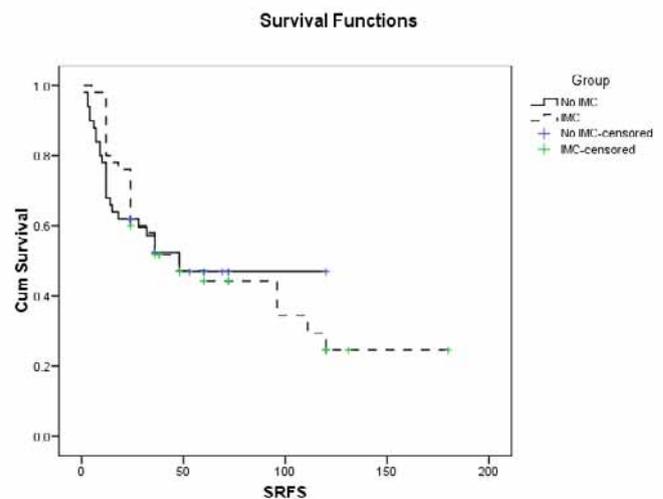


Fig 3: Kaplan-Maier survival curve of systemic relapse-free survival in both groups ($P=0.836$)

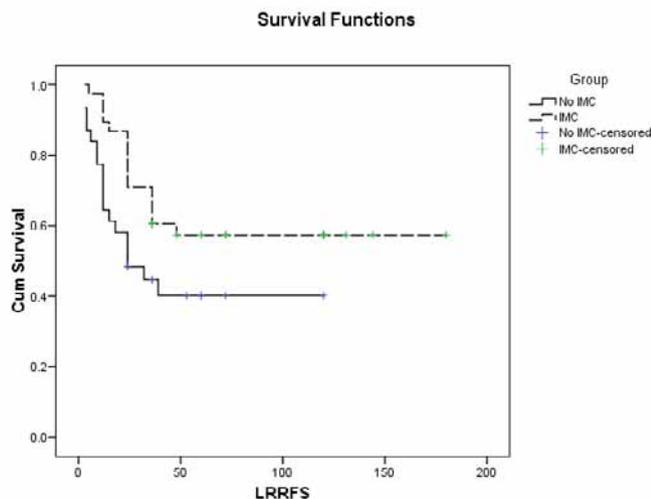


Fig 4: Kaplan-Meier survival curve of locoregional relapse-free survival of patients with N2-N3 stage (P=0.049)

Regarding the pattern of relapse in both groups, there was no documented IMC relapse or recurrence whether isolated or combined with any form of locoregional or systemic relapse. Moreover, the 48 patients in group A and the 44 in group B with documented locoregional relapse had no nodal recurrences (only breast or chest wall recurrences). Systemic relapse or distant metastasis was detected in 50 patients in group A compared to 62 patients in group B where bones, lung and liver were the most common affected sites in both groups.

Discussion

The significance of internal mammary lymph node as a second lymph node basin in breast cancer where 8%~37% tumors drain to IMC while 1%~5% of tumor exclusively drain to the IMC had been recognized as a major prognostic factor historically. It was reported that 54% of central and inner quadrant tumors and 18% lateral quadrant tumors were associated with positive IMC while 44% of cases with positive axillary lymph nodes had positive IMC (13-17). IMC involvement was found to be 4% to 65% during surgery, 8% to 27% during sentinel node biopsy, and 13% to 37% on lymphoscintigraphy (18). Following surgery, the value of IMLN irradiation without ignoring the risk of cardiac morbidity remains unclear presently while the prognostic significance of IMC recurrences were scarce and controversial (19). IMNR has been associated with compromised cosmetic outcome. With a separate IMN field, matchline fibrosis between the tangential and internal mammary field may compromise cosmetic outcome (11).

The existing literature contains conflicting data regarding the effects of treatment to the IMC on local control and overall survival (20-21). Surgical treatment of the IMC with en-bloc excision (the extended radical mastectomy) is now rarely performed in light of large randomized trials that failed to show a significant survival advantage from the technique (22-23). However, subsequent single-country re-analyses of the European surgical series have complicated the situation by arriving at contradictory conclusions (10). The effects of RT are even more controversial, with different studies leading to divergent conclusions. For example, Grabenbauer et al, observed IMN radiation reduced distant metastases in patients with medial tumors with a hazard ratio of 1.6 compared with patients

without IMN radiation (P=.02) (24). Le et al, reported equivalent overall and metastases-free survival for 330 patients with medial tumors as for 492 patients with lateral tumors when IMN radiation was given for medial tumors (25).

In our center, the majority of patients were treated with a separate IMC field till the late-1990s, regardless of whether they were node-positive or node-negative. Starting from the early-2000s, a shift in the treatment technique took place, in which separate IMC fields were not routinely employed regardless the number of involved axillary nodes or tumor location. This change in treatment technique over time afforded an opportunity to evaluate the potential benefit, or lack thereof, of irradiating the IMC.

Although the current study is a retrospective one, the data demonstrated no significant benefit to postoperative irradiation of IMC with separate field. However, it should be noted that, firstly, when these nodes are not intentionally targeted with a separate field, a proportion of the IM nodes are often included in the tangential and/or the supraclavicular fields. Lymphoscintigraphic studies by Recht et al. have revealed that 80% of IM nodes are located within the first three intercostal spaces, and 50% of all IMNs are located within 1 cm from midline (26). Therefore, the current practice of treating node positive patients with tangential fields with a medial border at midline matched to a supraclavicular field may in fact have included a significant portion of the potentially critical IMNs. Secondly, patients in whom the internal mammary nodes were not intentionally targeted were treated in a more modern era and were therefore more likely to receive more effective adjuvant systemic therapy. In addition, T3-T4 tumors (advanced stage of disease) were more likely to be encountered in group B patients (68%) compared with (38%) in group A patients. All these factors may give patients who did not receive postoperative irradiation of IMC with separate field a more favorable prognosis.

The current study failed to demonstrate a benefit or positive impact on survival parameters in patients received irradiation of IMC with separate field. However, subgroup analysis revealed that the benefit of IMC irradiation was limited to patients with 4 or more positive axillary lymph nodes (N2-N3) as evidenced only by a statistically significant better LRRFS. Furthermore, there was a trend toward a better OS in N2-N3 patients who received a separate IMC field but it did not reach the statistical significance. No similar benefit was observed among patients with medial breast tumors. The pattern of relapse in both groups was not different. There was no documented IMC relapse or recurrence whether isolated or combined with any form of locoregional or systemic relapse.

Similar results were reported by Freedman et al, who conducted a study to critically review both historical and new evidence concerning the incidence of IMN metastases, and the results of treatment of this region from randomized clinical trials. Treatment of IMC has not been shown to contribute to a survival benefit and Irradiation of the IMN chain in conjunction with the chest wall and supraclavicular region should be considered only for those with pathologically proven IMNs with the goal of improving tumor regional control (21). Taghian et al, examined the self-reported practice patterns of radiation oncologists in North America and Europe regarding radiotherapy to the IMC in breast cancer patients. A survey questionnaire was sent to physician members of the American Society for Therapeutic Radiology and Oncology (ASTRO) and European Society for Therapeutic Radiology and Oncology (ESTRO) regarding their management of breast cancer. Respondents were asked whether they would treat the IMC in several clinical scenarios. A total of 435 responses were obtained from European and 702 responses from North American radiation oncologists. Respondents were

increasingly likely to report IMC irradiation in scenarios with greater axillary involvement. Responses varied widely among different European regions, the United States, and Canada ($p < 0.01$). European respondents were more likely to treat the IMC ($p < 0.01$) than their North American counterparts. Academic physicians were more likely to treat the IMC than those in nonacademic positions ($p < 0.01$). The results of this study revealed significant international variation in attitudes regarding treatment of the IMC. The international patterns of variation mirror the divergent conclusions of studies conducted in the different regions, indicating that physicians may rely preferentially on evidence from local studies when making difficult treatment decisions. These variations in self-reported practice patterns indicate the need for greater data in this area, particularly from international cooperative trials (10).

Thus, with the available literature and its controversies and uncertainties, there is no clearly defined standard of care with respect to the appropriate treatment or exclusion of the internal mammary chain in the management of breast cancer. A more rational approach to breast cancer management might be determined by reviewing the available evidence and balancing the potential benefit of irradiating the IMC against the potential added toxicity with modern RT techniques.

Conclusion

Postoperative irradiation of IMC with separate field has no benefit with respect to survival parameters in breast cancer patients. It may be considered for patients with N2-N3 stage for better locoregional control

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