Long-term Survival Outcomes Following Internal Mammary Node Irradiation in Stage II-III Breast Cancer: Results of a Large Retrospective Study With 12-Year Follow-up

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Received Aug 23, 2012, and in revised form Feb 2, 2013. Accepted for publication Feb 23, 2013

Summary
This retrospective study explores the role of internal mammary node irradiation (IMNI) in a large cohort of patients after mastectomy and adjuvant chemotherapy with long-term follow-up. IMNI significantly improved disease-free survival, especially in patients with N2 disease and those with inner/central tumors.

Purpose: To examine the effect of internal mammary node irradiation (IMNI) on disease-free survival (DFS) and overall survival (OS) in breast cancer patients treated with modified radical mastectomy and postoperative radiation therapy.

Methods and Materials: Between 1994 and 2002, 396 patients with stage II-III breast cancer were treated with postmastectomy radiation therapy with (n = 197) or without (n = 199) IMNI. Patients who received neoadjuvant chemotherapy were excluded. IMNI was administered at the clinical discretion of the treating physician. Median RT dose was 50.4 Gy (range, 45.0-59.4 Gy) in 28 fractions, with inclusion of the supraclavicular fossa in 96% of patients. Adjuvant chemotherapy was administered to 99.7% of the patients and endocrine therapy to 53%.

Results: The median follow-up was 149 months (range, 124-202). IMNI patients had more advanced nodal stage and non-high grade tumors than those without IMNI (P < .001). Otherwise, disease and treatment characteristics were well balanced. The 10-year DFS with and without IMNI was 65% and 57%, respectively (P = .05). Multivariate analysis demonstrated that IMNI was an independent, positive predictor of DFS (hazard ratio [HR], 0.70; P = .02). Benefits of IMNI in DFS were seen most apparently in N2 patients (HR, 0.44; 95% confidence interval [CI], 0.26-0.74) and inner/central tumors (HR, 0.55; 95% CI, 0.34-0.90). The 10-year OS with and without IMNI was 72% and 66%, respectively (P = .62). The 10-year DFS and OS were 61%, and 69%, respectively.

Conclusions: Internal mammary node irradiation significantly improved DFS in postmastectomy breast cancer patients. Pending long-term results from randomized trials, treatment of
Introduction

The survival benefits of postmastectomy radiation therapy (PMRT) in node-positive breast cancer have been established in multiple randomized trials (1-3). All of these trials used internal mammary node irradiation (IMNI). However, available data on IMNI are conflicting (4-9). The National Cancer Institute of Canada MA-20 trial, which was presented at the annual meeting of American Society of Clinical Oncology 2011, demonstrated that the addition of regional radiation therapy (RT) including IMNI improved disease-free survival (DFS) in 1 to 3 positive node patients treated with breast conservation therapy (10). In contrast, a French randomized trial, which was presented at ASTRO 2009, showed no survival benefit associated with IMNI (9).

Because of the absence of strong evidence for or against treatment of the internal mammary node (IMN), there is a marked discrepancy in IMN treatment worldwide. Variable patterns of practice regarding IMNI were reported in North America and Europe (11), with physicians in European regions more likely to treat the IMN than North American radiation oncologists. Separate analysis looking at PMRT practice patterns in Korea has demonstrated half of patients received IMNI regardless of tumor stage (12).

In our institutions, despite a lack of formal guidelines within PMRT on whether or not to treat IMN, there has been a consistent discrepancy among treating physicians over the past 2 decades: physicians who prefer the electron beam to treat the chest wall have invariably included the IMN in the treatment field, whereas those who prefer the tangential field technique have not. In this study, we retrospectively reviewed patients with stage II-III breast cancer who were treated with modified radical mastectomy (MRM) and postoperative RT to examine the effect of IMNI on long-term survival outcomes and to highlight patient subsets who would benefit most from IMNI.

Methods and Materials

Study population

We identified 396 patients with stage II-III breast cancer who were treated with MRM and postoperative RT between October 1994 and January 2002 at 2 major academic centers in Korea. Patients who received neoadjuvant systemic therapy were excluded. All data regarding disease and treatment characteristics were retrospectively reviewed. Follow-up was performed from the medical records and/or communications with the patients and their family members.

Pretreatment evaluation consisted of a complete history/physical examination, complete blood count, chest x-ray, mammography, breast ultrasound, bone scan, and computed tomography (CT) scans of the abdomen/ chest if indicated.

Treatment

All patients underwent MRM with axillary lymph node (LN) dissection. Among them, 334 patients (84.3%) underwent surgery at the 2 study center hospitals and 62 (15.7%) were referred from community hospitals for RT consultation after surgery. The median number of removed axillary LNs was 22 (range, 4-79), with a median number of 8 metastatic LNs (range, 0-69). Most patients (97.2%) received appropriate axillary surgery in which 10 or more LNs were dissected.

After surgery, adjuvant chemotherapy (median 6 cycles; range, 2-9) was administered in all cases except for 1 patient who declined because of advanced age. The majority of patients (86.6%) received either CMF (cyclophosphamide, methotrexate and fluorouracil)-based or anthracycline-based chemotherapy, and the other patients (13.4%) received taxane-based therapy. A total of 208 patients (52.5%) with estrogen receptor (ER)- or progesterone receptor (PR)-positive tumors received adjuvant endocrine therapy. Tamoxifen was mostly used for 5 years after completing chemotherapy.

Postoperative RT with (n = 197) or without (n = 199) IMNI was generally given 4 weeks after completion of the last cycle of chemotherapy. CT scans were performed in all patients for RT planning. Median RT dose was 50.4 Gy (range, 45-59.4 Gy) in 28 fractions, with inclusion of the supraclavicular fossa in 96% of patients. In the IMNI patients, the ipsilateral supraclavicular node (SCL), infracavicular node (ICL), axillary LN, and lateral chest wall were treated by photon beam reverse hockey stick field, and the IMN and medial chest wall sites were treated by anterior 9 or 12 MeV electron beam field, which was tightly junctioned to the photon beam field (Fig. 1a). The 80% isodose curve was placed at the anterior pleural line and 0.5 cm beneath the IMNs, and an individual custom-made bolus was prepared to compensate for differences in chest wall thickness to reduce the irradiation dose to lung/heart (14). A moving junction technique was used at 25.2 Gy to improve dose homogeneity. In the non-IMNI patients, the chest wall was treated by 2 tangential photon beams and the ipsilateral SCL and ICL were treated by anterior photon beam (Fig. 1b). The bolus was applied over mastectomy scar sites with adequate margins. The supraclavicular field was omitted in 16 patients with N0 disease. The inclusion of IMN in the treatment volume was verified by a slice-by-slice review regarding isodose curve and the location of IMNs.

Data and statistical analysis

We documented all recurrences as first events by retrospective review of medical charts, radiologic images, and/or histologic confirmation. Histologic confirmation was done in 14.9% of our patients. Local recurrence was defined as recurrence of the disease at the chest wall. Regional recurrence was defined as that occurring in the SCL/ICL, axilla LN, or IMN. Distant metastasis (DM) was defined as any other site of recurrence.

We studied the following endpoints: DFS (defined as the length of time from date of first treatment to relapse or death; whichever came first) and overall survival (OS, defined as the length of time from date of first treatment to death from any cause). For statistical analysis, the Kaplan-Meier method was used to calculate the survival curve, and comparisons were made with log-rank test. Multivariate analysis and multiple subgroup analyses were performed with the Cox’s regression model. We selected all available
variables and carried out multivariate analysis using backwards elimination with a large alpha level (0.20) to stay in the model. $P$ values $\leq 0.05$ were considered significant. Statistical analysis was carried out using SPSS version 18.0.0 (SPSS, Chicago, IL).

**Results**

**Patient characteristics**

Data on patient characteristics are listed in Table 1. The median age was 45 years (range, 21-77 years). All tumors were confirmed histologically to be invasive carcinoma (ductal 91.2%, lobular 3.5%, and others 5.3%). According to the seventh edition of the American Joint Committee on Cancer staging system, 89.7% of the patients had locally advanced stage III breast cancer (stage IIA, 3.0%; stage IIB, 7.3%; stage IIIA, 50.3%; stage IIIB, 1.0%; and stage IIIC, 38.4%). IMNI patients had more advanced nodal stage and non-high-grade tumors than non-IMNI patients ($P<0.01$). Otherwise, disease and treatment characteristics regarding median follow-up time (IMNI vs non-IMNI, 148 vs 150 months), age, laterality, tumor location, T stage, median radiation dose (50.4 Gy vs 50.4 Gy), ER status, PR status, and use of adjuvant hormonal therapy were well balanced (all $P>0.05$). The median number of LNs removed from the axillary dissection was 23 in IMNI patients (range, 4-76) and 22 in non-IMNI patients (range, 4-60).

**Survival**

The median follow-up was 149 months (range, 124-202). Any type of recurrences occurred in 170 patients and 132 died: with recurrence ($n=127$) or without recurrence ($n=5$). The median DFS and OS were not reached. The 10-year DFS and OS were 61% (95% confidence interval [CI], 56%-66%) and 69% (95% CI, 65%-74%), respectively. The 5- and 10-year DFS was 75% (95% CI, 69%-81%) and 65% (95% CI, 59%-72%), respectively, with IMNI, and 64% (95% CI, 57%-70%), and 57% (95% CI, 50%-64%) without IMNI ($P=0.05$) (Fig. 2). The 5- and 10-year OS was 81% (95% CI, 76%-87%) and 72% (95% CI, 66%-79%), respectively, with IMNI, and 80% (95% CI, 75%-86%), and 66% (95% CI, 60%-73%) without IMNI ($P=0.62$) (Fig. 3).

**Multivariate analysis**

Multivariate analysis demonstrated that the independent prognostic factors for DFS were younger age ($<45$ vs $\geq 45$ years), advanced N stage (N3 vs N0-2), and use of IMNI (Table 2). Only advanced N stage was identified as independent prognostic factor for OS.

**Subgroup analysis**

Subgroup analysis showed that the effect of IMNI was consistently similar regardless of the patient’s age, T/N stage, histologic grade, tumor grade, ER/PR status, or the use of hormone therapy (all HR<1). However, an effect of IMNI on DFS was evident when stratified by N stage and tumor location.

Patients were categorized by nodal status into 3 groups: pathologic N0-1 ($n=64$) versus N2 ($n=180$) versus N3 ($n=152$). The HR of DFS by IMNI was 0.65 (95% CI, 0.28-1.53) in N0-1 patients, 0.44 (95% CI, 0.26-0.74) in N2 patients, and 0.98 (95% CI, 0.63-1.52) in N3 patients. When patients’ survival data were analyzed based on the breast tumor location, the HR of DFS was 0.55 (95% CI, 0.34-0.90) in 141 patients with inner/central breast cancers and...
0.86 (95% CI, 0.58-1.27) in 255 patients with outer breast cancers. Similar patterns were observed in overall survival, but it did not reach to statistical significance in any condition (all \( P > .05 \)).

**Pattern of recurrence**

Pattern of tumor recurrence was recorded for the first relapse site only (Table 3). We observed a significantly decreased incidence of any type of recurrence in IMNI group than non-IMNI group (\( P = .04 \)). Local recurrence rate was same in 2 groups as 4%. Patients in the IMNI group had lower regional recurrence (7% vs 11%) and distant metastasis (35% vs 43%) rates than those in non-IMNI, but this was not statistically significant. The IMN recurrence was 1 and 4 for the IMNI and non-IMNI groups, respectively. DM was the dominant type of first relapse, accounting for 39% of recurrences in the entire cohort.

**Discussion**

Although IMN involvement in breast cancer is not rare and shows a correlation with poor prognosis, IMNI has been abandoned for a long time. The reasons were that clinically apparent IMN failure was not frequently seen and there was no definite evidence of beneficial effect of IMNI. In addition, the risk of treatment-related cardiovascular morbidity and mortality was another concern. However, IMN metastasis at diagnosis or during the follow-up period is now detected more frequently by CT, positron emission tomography, ultrasonography, or magnetic resonance imaging, and as a result, this issue has recently attracted more attention from oncologists treating breast cancer.

The importance of regional RT was emphasized by the recent interim data of a prospective multicenter randomized study (the Canadian MA-20 trial) (10). This study randomized 1832 patients who underwent breast conservation surgery to receive whole breast irradiation alone or with regional node irradiation (SCL, IMN, and high-risk axilla LN). Most patients had N1 disease (85%) and received adjuvant chemotherapy (91%) and hormone therapy (71%). The additional regional node irradiation significantly decreased DM as well as locoregional recurrence with a trend toward improved OS.

Several studies (including preliminary data of 1 randomized trial, 1 population-based study, and 3 retrospective studies) have explored the role of IMNI in breast cancer (6-10). A second set of interim data of a phase 3 trial from France showed no survival benefit associated with IMNI in patients with early stage breast cancer. This study randomized 1334 stage I-II breast cancer patients who underwent mastectomy to receive elective IMNI or not (9). Most patients were node-positive (75%) and received adjuvant treatment (86%). Although no recurrence data were presented in this interim analysis, there was no significant difference in 10-year OS between the 2 groups. Most importantly, there was no increase in cardiac toxicity in IMNI patients.

Similarly, a population-based analysis from British Columbia showed that IMNI was not associated with a significant survival benefit from the cohort of 2413 breast cancer patients with N1 or...
T3/4N0 disease, consisting of 62% of the mastectomy patients (15). However, this study suggested that IMNI in N1 patients may result in improved clinical outcomes (a nonsignificant 3% survival benefit). There were several possible explanations for these results, such as unintentional inclusion of IMNs in non-IMNI group, and an imbalance in comorbidity between the 2 groups.

Several retrospective studies have reported diverse results. Stemmer et al performed a secondary analysis of a phase 2 prospective trial with 100 patients with high-risk stage II-IIIA breast cancer after high-dose chemotherapy and stem cell support (8). In this study, 54% of patients received a mastectomy, and 46% underwent breast conservation surgery. IMNI was not given to 33 patients because the delivering electron beam was unavailable for part of the period under study. The data showed a significant improvement in 5-year DFS in patients who received IMNI compared with those without IMNI and a borderline improvement in 5-year OS.

In contrast, 2 large-scale, retrospective studies concluded that the addition of IMNI resulted in no significant benefit in terms of OS and DM-free survival (6, 7). However, caution is needed in interpreting these results because the IMNI group included significantly more patients with potential risk factors such as T2 disease, positive LN, medial tumors, indeterminate resection margins, and longer follow-up time than the non-IMNI group. A multivariate analysis was not performed in either study.

Although our study is retrospective in nature, it has several strengths: (1) As in Stemmer’s study, the determination of IMNI treatment was influenced by culture-driven factors, which minimizes selection bias. In addition, the number of patients was evenly distributed among the 2 treatment groups; (2) Homogenous radiation techniques were applied in each treatment group from 2 centers, which lessens the confounding effects caused by various radiotherapeutic techniques. Also, our IMNI technique using electron beam with an individualized custom bolus obviated the risk of increased cardiac and lung toxicities (14, 16); and (3) All patients except 1 received adjuvant chemotherapy after surgery and all were followed for a minimum of 10 years or until death. This enables us to evaluate the long-term effect of IMNI when used in conjunction with chemotherapeutic agents.

In our study, a decreased incidence of both regional recurrence and DM as first failure was observed in IMNI patients. Similar to an update of Danish Breast Cancer Cooperative Group 82 b/c trials that supported the Halstedian hypothesis (3), our findings indicated that enhancing regional node control by IMNI combined with chemotherapy not only improved locoregional control, but also prevented secondary dissemination to distant organs after locoregional recurrences. This effect was evident in patients with inner/central tumors or with less tumor burden in node area, but was negligible in patients with outer tumors or with N3 disease.

This observation may be explained by findings from several lymphoscintigraphy studies showing that inner/central tumors (18%-63%) drain more frequently to the IMN than outer tumors (5%-16%) (17-19). Huang et al aimed to identify patients at high risk of IMNI metastasis by analyzing 2269 breast cancer patients who were treated with extended radical mastectomy (17). Of 537 patients with 1 to 6 positive lymph nodes, those with inner/central tumors had higher rates of IMN metastasis than those with outer tumors (30% vs 16%). However, among 258 patients with >7 positive lymph nodes the incidence of IMNI metastasis was high for both inner/central and outer tumors (40% vs 43%). Kong et al reported that IMN drainage on preoperative lymphoscintigraphy was significantly related to an increased risk of DM (18).

In our cohort, it is not clear why an improved DFS did not translate into a significantly prolonged OS; however, several reasons (eg, small number of patients and retrospective study design) may be associated with this finding. In our opinion, the most plausible explanation is the relatively long-term survival

**Figure 3.** Overall survival (OS) among all study patients treated with or without internal mammary node irradiation (IMNI).

![Image](image.png)

**Table 2** Multivariate analysis for disease-free survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subgroups</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>&lt;45 vs ≥45</td>
<td>1.40</td>
<td>1.03-1.90</td>
<td>.03</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Inner/central vs outer</td>
<td>1.24</td>
<td>0.91-1.69</td>
<td>.17</td>
</tr>
<tr>
<td>N stage</td>
<td>N3 vs N0-2</td>
<td>1.86</td>
<td>1.37-2.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IMNI</td>
<td>Yes vs no</td>
<td>0.70</td>
<td>0.52-0.96</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI = confidence interval; HR = hazard ratio; IMNI = internal mammary node irradiation.

**Table 3** Site of first tumor recurrence

<table>
<thead>
<tr>
<th>Site</th>
<th>No. (%) of patients with recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMNI (n = 197)</td>
</tr>
<tr>
<td>Any*</td>
<td>74 (37.6)</td>
</tr>
<tr>
<td>Locoregional</td>
<td>19 (9.6)</td>
</tr>
<tr>
<td>Local</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Regional</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>IMN</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Distant</td>
<td>69 (35.0)</td>
</tr>
</tbody>
</table>

**Abbreviations:** IMN = internal mammary node; IMNI = internal mammary node irradiation.

* P < .04.
after recurrence. The median time to death after recurrences was 27 months (95% CI, 20.3-33.7 months). We did not collect any toxicity data. However, late cardiac toxicity should be evaluated whether IMNI in left breast cancer has any effect on it in future study with longer follow-up periods. Another drawback of current study is imbalances in N stage and tumor grade distribution between the 2 groups, which may have obscured the results. A small number of N0-1 patients limited analysis in this subset, which may be important because some high-risk N0 and N1 patients may benefit from IMNI, but we cannot answer this question.

In conclusion, treatment of IMNs improved long-term DFS in locally advanced breast cancer patients treated with PMRT. Benefits of IMNI were seen most obviously in N2 patients and inner/central tumors. However, randomized controlled trials are needed to clearly define the role of IMNI in RT for breast cancer and its long-term effect on survival and toxicity. The European Organisation for Research and Treatment of Cancer 22,922/10,925 and the National Cancer Institute of Canada MA-20 trials are assessing the benefit of regional RT including IMNI (10, 20). The Korean Radiation Oncology Group initiated a phase 3, multi-institutional, randomized trial (KROG-0806) in 2008. In this trial, 748 node-positive patients after mastectomy or breast conservation therapy were randomly assigned to receive RT either with or without IMNI. In breast-conserved patients, treatment of IMN is more complicated, especially for left-sided breast cancer. Contemporary RT techniques including deep inspiration breathing hold and intensity modulated RT have been investigated to minimize cardiac exposure. Pending long-term results from randomized trials, IMNI should be considered in PMRT patients.

References
