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Original Article

Postmastectomy internal mammary node radiation in women with breast cancer: a long-term follow-up study

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Abstract

Background: To observe the impact of internal mammary node irradiation (IMNI) on disease-free survival (DFS) and overall survival (OS) in postmastectomy women with breast cancer.

Materials and methods: Between 1978 and 1996, 153 women with stage II–III breast cancer were treated with postmastectomy radiation therapy (RT) with IMNI. Their clinical, pathological and treatment characteristics were matched with 166 patients without IMNI. The RT dose was 35 Gy to the chest wall and 40 Gy to the supraclavicular fossa and IMN in 15 fractions over 3 weeks with photons. All patients were planned with two-dimensional technique. Adjuvant chemotherapy was administered to 41% and endocrine therapy to 52% of the patients. Symptomatic patients were further assessed for late pulmonary and late cardiac effects.

Results: The median follow-up period was 203 months (range, 182–224), and the median age was 44 years (range 20–73 years). The IMNI group had significantly more right-sided and inner/central quadrant tumours. Other characteristics were comparable between both the groups. DFS at 15 years with and without IMNI was 64 and 49%, respectively ($p = 0{\cdot}0001$). On multivariate analysis, IMNI was an independent, positive predictor of DFS [hazard ratio (HR), 2·89; $p = 0{\cdot}0001$]. Benefit of IMNI on DFS was more apparent in inner/central tumours [HR, 1·48; 95% confidence interval (CI), 1·02–2·88], N2–N3 patients (HR, 1·44; 95% CI, 1·09–2·10) and in those who received chemotherapy (HR, 1·70; 95% CI, 1·07–2·71). OS at 15 years with and without IMNI was 68 and 54%, respectively ($p = 0{\cdot}0001$). Late pulmonary toxicity was 1·5 versus 1% with and without IMNI, respectively. Late cardiac toxicity was 2·6 versus 1·8% with and without IMNI, respectively.

Conclusions: IMNI significantly improved DFS and OS in postmastectomy breast cancer patients. Benefit of IMNI was seen in patients with central/inner tumours and N2–N3 disease. Late cardiopulmonary toxicities were comparable between the two groups.

Keywords: breast cancer; internal mammary node; mastectomy; radiation

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INTRODUCTION

The internal mammary nodes (IMN) are a potential site for locoregional spread from breast cancer.[1] IMN may be involved in a substantial proportion of cases, particularly in patients with involved axillary nodes, large and central/inner tumour location. In axillary node-negative patients, the risk of positive IMNs is 6–9% and it is 28–52% for axillary node-positive patients.[2–6] In axillary node-positive patients, inner quadrant tumours have been associated with rates of IMN positivity of 44–65% compared with only 19–42% for outer quadrant tumours. In axillary node-negative patients, the IMNs were positive in 12–14% of inner quadrant tumours compared with 3–8% of outer quadrant tumours.[2,3,5,6]

Clinical recurrences in the IMN region are uncommon or are not recognised, perhaps because of being associated with metastases to other parts. Many trials have established the role of postmastectomy radiation that included internal mammary node irradiation (IMNI)[7,8], but controversy still exists regarding the treatment of this region.[9–11] All these patients may not require locoregional therapy.[12] Radiation oncologists who irradiate IMN think that these may be a reservoir for cancer cells with potential for recurrence, a source of distant metastases and ultimately may compromise the survival of the patients.[13] Oncologists who are against IMNI are concerned about the late effects to the heart and lungs.[14–16] However, studies that showed excess risk of death due to cardiac morbidity were carried out on patients treated with outdated radiation technology from retrospective studies and are statistical projections rather than concrete evidences.[17,18] These studies were carried out before the doxorubicin and trastuzumab era, and therefore it will be difficult to draw concrete conclusions from these studies. Late cardiac effects of radiation therapy are mainly due to occlusion of the left anterior descending artery and the right coronary artery, but muscle damage can also lead to cardiomyopathy. The advent of effective systemic chemotherapy has also been one of the factors leading to the decreased use of IMNI during the past two decades. The paclitaxel-based regimen reduced recurrence by 17%.[19] One year of trastuzumab treatment reduced the risk of disease recurrence by 24% in HER2-positive breast cancer patients.[20]

Elective IMNI is not indicated as a component of breast cancer treatment since the last two decades because of the conflicting data, less IMN failure and no beneficial effect of IMNI.[9,10] Therefore, IMNI is a controversial area in breast cancer management. The recently published positive trials testing postmastectomy radiation that had included regional IMNI has renewed interest in IMN elective treatment.[21,22] Recent lymphoscintigraphy data also indicate that selected early-stage breast cancers have high rates of primary lymphatic drainage to the IMN, particularly tumours located in the central and inner quadrant.[23] IMN metastases at diagnosis or treatment are now detected more frequently by CT, positron emission tomography and magnetic resonance imaging, and thus it is gaining more attention from oncologists treating breast cancer. The purpose of this retrospective analysis was to observe the impact of IMNI on disease-free survival (DFS) and overall survival (OS) in women with breast cancer treated with mastectomy and postoperative locoregional radiation therapy (RT).

MATERIALS AND METHODS

Study population

Between 1978 and 1996, 153 women with stage II–III breast cancer were treated with postmastectomy RT with IMNI. In all the patients, a detailed analysis was carried out for age, menopausal status, co-morbidity, tumour laterality, location, stage, surgery, RT technique, dose, the use of chemotherapy or hormonal therapy and other clinical and/or pathologic characteristics, as shown in Table 1. All parameters were entered into a computerised database. Clinical, pathological and treatment-related characteristics of patients with IMNI were matched with 166 patients who were not given IMNI during those years.

Surgery

All the patients underwent surgery, either modified radical mastectomy or total mastectomy with axillary dissection.

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Table 1. Patient characteristics

Characteristics	IMNI (153) No. (%)	Non-IMNI (166) No. (%)	*p*
Age			0·88
<40	34 (22)	35 (21)	
≥40	122 (78)	131 (79)	
Menopausal status			0·08
Premenopausal	100 (65)	93 (56)	
Postmenopausal	53 (35)	73 (44)	
Laterality			<0·001
Right	140 (91·5)	106 (64)	
Left	13 (8·5)	60 (36)	
Quadrant			0·002
Outer	100 (67)	135 (81)	
Inner/central	51 (33)	31 (19)	
Co-morbidity			0·20
Yes	7 (4·5)	3 (2)	
None	146 (95·5)	163 (98)	
Tumour			1·0
T1T2	96 (63)	106 (64)	
T3T4	57 (37)	63 (36)	
Surgery			0·07
MRM	14 (9)	26 (16)	
TMAC	139 (91)	140 (84)	
Histology			0·75
IDC	137 (90)	150 (90)	
ILC	8 (5)	6 (4)	
Others	8 (5)	10 (6)	
Grade			0·88
I and II	132 (86)	144 (87)	
III	21 (14)	22 (13)	
DRP			0·52
Yes	21 (14)	27 (16)	
No	132 (86)	139 (84)	
LVI			0·13
Yes	13 (9)	23 (14)	
No	140 (91)	143 (86)	
Node			0·47
0	78 (51)	71 (43)	
1	55 (36)	66 (40)	
2 and 3	20 (13)	28 (17)	
ECE			0·80
Yes	10 (7)	12 (7)	
No	143 (93)	154 (93)	
ER			0·27
Positive	70 (46)	81 (49)	
Negative	28 (18)	32 (19)	
Unknown	54 (36)	53 (32)	
PR			0·342
Positive	52 (34)	61 (37)	
Negative	44 (29)	52 (31)	
Unknown	57 (37)	53 (32)	
Chemotherapy			0·28
Yes	67 (43)	63 (38)	
No	86 (57)	103 (62)	
Hormones			0·21
Yes	76 (49)	91 (55)	
No	77 (51)	75 (45)	

Abbreviations: IMNI, internal mammary node irradiation; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; DRP, deep resection plane; LVI, lymphovascular invasion; ECE, extracapsular extension; ER, oestrogen receptor; PR, progesterone receptor.

Radiotherapy

The patients were given radiation to the axilla and the supraclavicular region when axillary nodes were positive, axillary status was unknown or when incomplete/no axillary dissection was performed. An anterior photon field was used to deliver radiation to the supraclavicular, infraclavicular, axillary nodes and IMN. The two tangential opposed fields were used to irradiate the chest wall. The borders for chest wall radiotherapy were the anterior midline (medial), the midaxillary line (laterally), the inframammary fold (inferior) and the inferior to the head of the clavicle (superior). The supraclavicular, infraclavicular and high axillary lymph nodes were treated with an anterior photon field; the inferior portion of this field was matched to the superior edge of the tangent fields (Figure 1). The RT dose was 35 Gy to the chest wall and 40 Gy to the supraclavicular fossa in 15 fractions over 3 weeks with photons on cobalt or linear accelerator. The breast cone was used for patients treated on cobalt, which has a shielding block to reduce penumbra and dose to the lung. The doses were prescribed at the midpoint of the central axis. The head of the humerus was also shielded from the radiation beam in patients with adequate axillary dissection with <25% nodes involved. The bolus was applied on the chest wall on alternate days.

IMNI was administered at the clinical discretion of the treating physician; however, patients

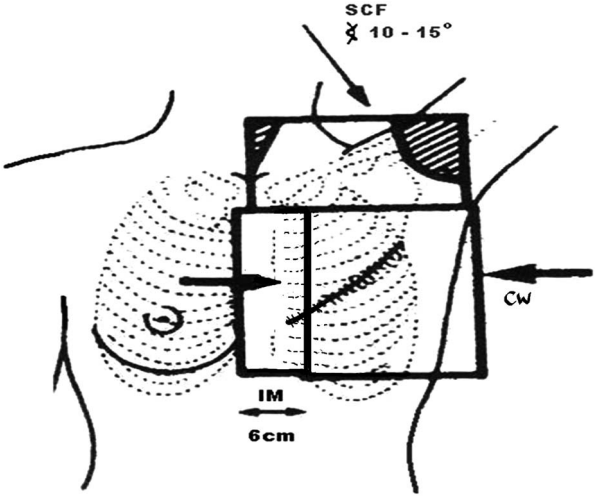

Figure 1. Radiation field marking.

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with T3, T4 tumours, tumours in the inner and central quadrants and ≥4 positive nodes in the axilla were given IMNI. Patients were planned with two-dimensional (2D) technique. IMNs were irradiated with a separate 14 × 6 cm field. The first five intercostal spaces were included in the IMN target volume. The medial border of the IMN field was midline; lateral border 5–6 cm lateral to the midline; the superior border abuts the inferior border of the supraclavicular field; and the inferior border was above the xiphoid. The RT dose delivered was 40 Gy/15#/3 weeks calculated at a point 4–5 cm beneath the skin surface. Treatment was given using ^{60}Co units or 4 MV linear accelerator.

Adjuvant systemic treatment

The two chemotherapy regimens used were CMF (cyclophosphamide: 600 mg/m^2, methotrexate: 40 mg/m^2 and 5-FU: 600 mg/m^2) in 123 (95%) patients and FAC (5-FU: 600 mg/m^2, adriamycin: 50 mg/m^2 and cyclophosphamide: 600 mg/m^2) in 7 (5%) patients. Tamoxifen was administered to 167 (52%) patients; the dose was 20 mg daily for 5 years.

Follow-up

The patients were followed-up at regular intervals (every 3 months up to 1 year, every 4 months up to 3 years, 6 months up to 5 years and yearly thereafter) and were further tested only if they had symptoms or evidence of recurrent disease or metastatic disease. Patients with cardiac and chest symptoms were subjected to ECHO and pulmonary function tests. The toxicity scoring was carried out using the RTOG scale.[24]

Statistical analysis

The end points analysed were DFS (time from date of first treatment to relapse or death) and OS (time from date of first treatment to death from any cause). The Kaplan–Meier method was used to estimate DFS and OS curves, and comparison was made using the log-rank test. The Cox's proportional hazard regression model was used for multivariate analysis and multiple subgroup analyses. p-values ≤0·05 were considered significant. The statistical analysis was carried out using SPSS version 18·0·0.

RESULTS

Patient characteristics

Patient characteristics were as shown in Table 1. Median age was 44 years (range 20–73 years). The median period of follow-up was 203 months (range, 182–224 months). Left-sided tumours were less in the IMNI group than in the non-IMNI group (8.5 versus 36%; p = <0·001). Inner/central quadrant tumour location was more in the IMNI group (33%) compared with patients without IMNI (19%) (p = 0·002). The other patient, tumour and treatment characteristics, such as age, co-morbidity, menopausal status, stage, surgery, pathological features, radiation dose and the use of chemotherapy and hormones, were comparable between both the groups.

Pattern of recurrence

The IMNI group had decreased incidence of all types of recurrence as shown in Table 2. Local recurrence was significantly lesser in patients with IMNI compared with patients without IMNI [5 (3·5%) versus 15(9%)] (p = 0·033). Regional recurrence rate was higher in patients without IMNI (4%) compared with patients with IMNI (1·5%) (p = 0·176). The IMN recurrence rate was 1 and 4% in patients with IMNI and without IMNI, respectively (p = 0·068). Distant metastases rate was significantly lesser in patients with IMNI compared with patients without IMNI [7 (12%) versus 39 (21%)] (p = 0·022).

Survival

The 15-year DFS (Figure 2) was significantly better in patients with IMNI (64%) compared with patients without IMNI (49%; p = 0·0001). Multivariate analysis (Table 3) demonstrated that IMNI was a strong positive predictor of DFS (HR, 2·89; 95% CI, 1·81–4·63, p = <0·001). Benefits of IMNI in terms of DFS were also apparent in central/inner quadrant tumours (HR, 1·48; 95% CI, 1·02–2·88), N2–N3 disease (HR, 1·44; CI, 1·09–1·90) and in those who received chemotherapy (HR, 1·70; 95% CI, 1·07–2·71), respectively. The 15-year OS (Figure 3) was also significantly better with IMNI compared with without IMNI, 68 versus 54%, respectively (p = 0·01).

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Late effects

Late effects were not statistically different between the two groups. Late grade >2 pulmonary toxicity was 1·5 versus 1% with and without IMNI, respectively. Late grade >2 cardiac toxicity was 2·6 versus 1·8%, respectively. Lymphoedema, grade >2, was seen in six patients in both the arms. Rib fracture was reported in two (1·5%) patients with IMNI and in one (0·5%) patient without IMNI (Table 4).

Table 2. Pattern of tumour recurrence

Site	No. (%)of patients with recurrence IMNI (n = 153)	Non-IMNI (n = 166)	p
Local	5 (3·5)	15 (9)	0·033
Regional	2 (1·5)	7 (4)	0·176
IMN	1 (1)	7 (4)	0·068
Distant	17 (12)	34 (21)	0·022

Abbreviations: IMNI, internal mammary node irradiation; IMN, internal mammary node.

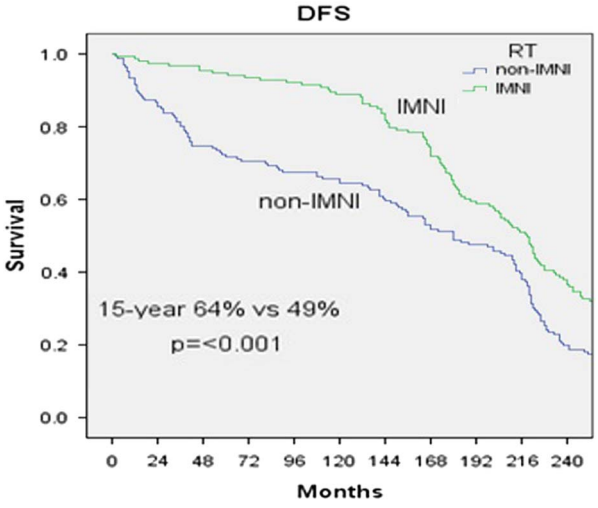

Figure 2. 15-year disease-free survival.

DISCUSSION

This retrospective study with long-term follow-up demonstrated a decreased incidence of both locoregional recurrence as well as distant metastases as first failure in postmastectomy patients with IMNI (Table 2). The study also demonstrated significant benefits in terms of DFS (Figure 2) and OS (Figure 3) with IMNI. The Danish 82b trial (which included treatment of the IMN) had also demonstrated that postmastectomy radiation improves the probability of survival in patients with high-risk breast cancer.[7] These findings indicated that enhancing regional control by IMNI not only improved locoregional control but also prevented secondary dissemination to distant organs. OS benefit appears to be a consequence of the reduction of distant metastasis rate rather than improved regional tumour control only, as indicated by the almost identical effect of regional radiotherapy on local disease and distant metastases (Table 2). IMNI may well represent the importance of eradication of an occult reservoir of disease that never becomes clinically significant but serves as a source for distant disease.

In a recent retrospective observational study from Korea of stage II and III breast cancer patients treated with postmastectomy radiation using 3D planning,[17] the authors concluded that there is a survival benefit from IMNI. They also found that benefits of IMNI in DFS were seen most apparently in N2 patients (HR, 0·44; 95% CI, 0·26–0·74) and inner/central tumours (HR, 0·55; 95% CI, 0·34–0·90). Our study also demonstrated significant DFS advantage in patients with inner/central tumours, N2–N3 disease and those who received chemotherapy (Table 3). However, a randomised French trial[25]

Table 3. Multivariate analysis for DFS

Variable	Subgroups	HR	95% CI	p
Age	<40 versus ≥40	1·22	0·89–1·46	0·21
Tumour location	Inner/central versus outer	1·48	1·02–2·88	0·032
N stage	N2–N3 versus N0–N1	1·44	1·09–2·90	0·009
IMNI	Yes versus no	2·89	1·81–4·63	<0·0001
Chemotherapy	Yes versus no	1·70	1·07–2·71	0·023

Abbreviations: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; IMNI, internal mammary node irradiation.

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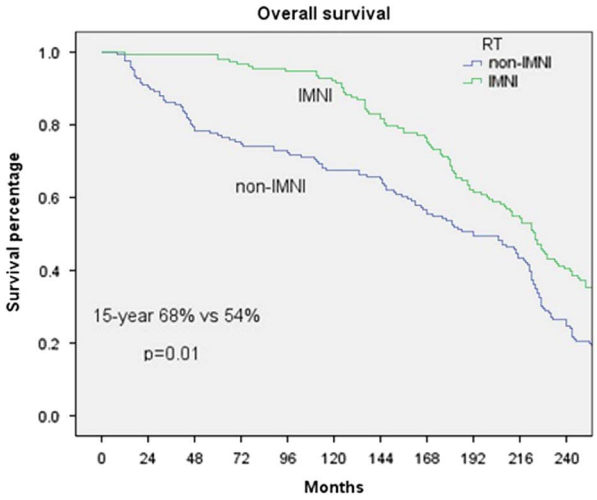

Figure 3. 15-year overall survival.

Table 4. *Late effects of radiation*

Late toxicity	IMNI [*n* (%)]	Non-IMNI [*n* (%)]	*p*
Lung			
Grade 2	6 (4)	5 (3)	0·18
Grade >2	2 (1·5)	2 (1)	0·21
Cardiac	4 (2·6)	3 (1·8)	0·07
Lymphoedema			
Grade 2	9 (5·5)	10 (6)	0·23
Grade >2	6 (4)	6 (3·5)	0·36
Rib fracture	2 (1·5)	1 (0·5)	0·54

Abbreviations: IMNI, internal mammary node irradiation.

failed to detect any survival benefit in post-mastectomy patients with IMNI. The French trial had its own limitations in that it was substantially underpowered to detect a difference of the magnitude that would reasonably be expected in these circumstances. In addition, the trial included node-negative patients, a population in whom the risk of IMN involvement is lower, <10%, and whose inclusion decreases the ability of the trial to detect a meaningful difference in a more appropriately selected, higher-risk population. The strength of our study lies in standard radiotherapy dose fractionation delivered to all the patients with single modality. Our study also had a longer follow-up period, median 16 years, compared with the French (11 years) and Korean (12 years) trials, respectively. We also reported associated co-morbidities and included patients with advanced stage disease as well.

Other trials that have gathered more reliable evidence to inform the appropriate approach towards radiation management of the regional nodes are National Cancer Institute of Canada MA.20 and European Organization for Research and Treatment of Cancer (EORTC) 10925, but the final results of these trials are yet to be reported. The preliminary results of the MA.20 suggest that regional RT may be particularly important, with a reduction in distant metastases that was even greater than the reduction in regional recurrence rates.[26] Regional radiotherapy improved regional tumour control at 5 years by 2·3%, but reduced the distant metastasis rate at 5 years by 5·4%. Our study also supports these findings with a significant reduction in distant metastases (from 21 to 12%) with IMNI. A recent meta-analysis of IMNI trials also concluded that absolute benefits in OS were 1·6% in the MA.20 trial at 5 years and 1·6 and 3·3% in the EORTC and the French trials at 10 years, respectively.[27] However, a population-based analysis from British Columbia showed that IMNI was not associated with significant survival benefit in 2,413 breast cancer patients with N1 or T3/4N0 disease. Nevertheless, this study also suggested that in patients with N1 disease, IMNI may lead to improved survival.[28] The limitations of the study were as follows: inclusion of the IMNs in the non-IMN group, an imbalance in co-morbidity between the two groups and N0 and N1 patients having lower incidence of IMN involvement. Although it is important to validate these findings in the EORTC trial, neither the Canadian nor European trials measured the impact of IMNI in isolation; therefore, they are unlikely to settle this debate fully, even when their final results are known. The other trial by Korean Radiation Oncology Group (KROG) 0806 does focus on IMNI specifically, but whether it is adequately powered to detect the impact of IMNI with only 748 patients is questionable.[29]

The late-term cardiopulmonary toxicity was not different in the two groups (Table 4). The follow-up of 16 years is long enough to report late cardiac effects of radiation. A possible explanation for low cardiac morbidity or mortality in our study may be due to fewer patients with left-sided tumours in the IMNI group (8·5%) compared with the non-IMNI group

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(36%), and the majority of patients (91%) received CMF base chemotherapy regimen, which is not cardiotoxic. IMNI was not associated with an excess of cardiac death or cardiac toxicity rate in any of the three recent trials as well.[19,20,23] Although the median follow-up of the MA.20 trial (62 months) has to be regarded as insufficient to exclude relevant late cardiac toxicity, the median follow-up periods of the EORTC 22922–10925 trial (10·9 years), French trial (11·3 years) and the present study (16 years) were long enough to conclude that even with the IMNI, cardiac toxicity remains probably low. Late cardiac toxicity may be a concern, especially in patients with left-sided breast cancer. However, with modern technology, it is possible to minimise radiation dose to the heart and lungs. The MA.20 and EORTC trials have reported statistically significant 1–3% increase in grade 1–2 late lung toxicity with IMNI. However, the addition of radiotherapy to the IMN did not result in higher rates of acute or late toxicities in the French trial.

The radiation oncologist should take into consideration the risk of IMN nodal involvement, patient's anatomy and ability to exclude critical normal structures from the treatment fields, so that clinical benefit of IMNI is delivered to the patient without causing harm. One of the goals of treatment is always to maintain quality of life (QOL) of the patients. Breast cancer patients receive multidisplinary treatment and each causes some form of morbidity. Surgery causes disfigurement and lymphoedema. Chemotherapy causes alopaecia, neuropathy, chemopause, cardiac injury and osteoporosis. Radiation may add to lymphoedema and cause cardiac and pulmonary toxicities if not properly planned and executed. Hormonal therapy causes osteoporosis, vascular problems and rarely second malignancy due to tamoxifen. The diagnosis of breast cancer and treatment may lead to psychosocial, sexual and occupational impacts. Therefore, during the course of treatment, all these complications and effects should be assessed and timely intervention should be carried out to maintain the QOL of these women with breast cancer.

From the findings of this retrospective study, we do not advocate IMNI in low-risk cases, such as cases of micrometastatic axillary involvement, but we believe that coverage of this region is worth pursuing in N2–N3 axillary involvement, particularly when the tumour is large and is medially located or when other high-risk features exist. With modern planning and treatment techniques, including consideration of respiratory motion control, it is possible to cover the IMNs in most patients, exposing the heart and coronary vasculature to only low-dose scatter.[8] Using these techniques, one can administer treatment to this region while sparing critical normal tissues; we believe it is important to include the IMNs in the treatment fields in patients with moderate to substantial risk of nodal involvement.

However, like any retrospective study, our study also carries the usual limitations. Ours was a single-institutional study, and thus selection bias may exist and apparent differences between patients who did and did not receive IMN radiation may not be causally related to the administration of treatment but rather confounded by other meaningful differences between the groups. Moreover, patient characteristics clearly did play some role in selection, with patients receiving IMN radiation having more advanced nodal disease. The majority of patients received CMF chemotherapy, and thus we cannot comment on the impact of anthracyclins, taxanes and trastuzumab interactions with IMNI. We believe that this study's findings of higher DFS and OS in patients receiving IMN radiation are intriguing and hypothesis-generating, although strong causal conclusions cannot be drawn from a study with this design. Ultimately, it is critical for radiation oncologists to continually re-evaluate our treatment approaches as results from well-designed and well-executed trials become available. Only by advancing our understanding of the impact of different treatments on breast cancer and OS, late toxicity and QOL we can optimise the recommendations we make to our patients in this complex and evolving area of practice.

CONCLUSIONS

IMNI significantly improved DFS and OS in postmastectomy patients with breast cancer. The benefit of IMNI was seen in patients with

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central/inner quadrant tumours, N2–N3 disease and those who received chemotherapy. Late effects were not statistically different between the two groups. However, being a retrospective study, selection bias may exist. The ongoing and pending final results of the EORTC, NCI and Korean trials may clearly define the role of IMNI and its long-term effects on survival and toxicity.

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