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Original Research Article

Postmastectomy internal mammary nodal irradiation: A long-term outcome

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ABSTRACT

Background and objective: The internal mammary lymph nodes (IMN) have been recognized as a potential site of regional breast cancer spread. The aim of this study was to evaluate the impact of internal mammary node radiotherapy (RT) to on clinical outcomes in breast cancer patients treated with mastectomy and postoperative radiation therapy.
Materials and methods: This cohort study included 588 patients with breast cancers located in the central and medial quadrants. IMN RT was applied to 320 patients and 268 patients did not receive it IMN RT. Inside the IMN RT group, 165 patients received external beam IMN irradiation (IMN-EB). Mastectomy combined with using Californium-252 neutron source implantation was applied to 155 patients (IMN-BT). Cox proportional hazards modeling was used to determine the influence of IMN RT on clinical outcome. Age, tumor size, lymph nodal status, adjuvant radiotherapy, chemotherapy and hormonal therapy were assessed.
Results: IMN-EB resulted in a significant improvement of distant metastasis-free survival, breast cancer-specific survival and overall survival ($P = 0.033$, $P = 0.037$ and $P = 0.011$, respectively). The IMN-EB radiotherapy has a significant impact on event-free survival (HR, 0.67; 95% CI, 0.46–0.91; $P = 0.043$) and breast cancer-specific survival (HR, 0.64; 95% CI, 45–0.91; $P = 0.013$) in patients with moderate-risk (stage $T_{1–2}$ N_1). There was no association between IMN RT and clinical outcomes of patients with high-risk disease (stage $T_{3–4}$ $N_{2–3}$) in any of the study end points.
Conclusions: The effects of IMN-EB radiotherapy on event-free survival and breast cancer-specific survival were benefit for women with moderate-risk breast cancer.

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1. Introduction

Postmastectomy radiotherapy clearly reduces the frequency of local regional recurrence in high-risk breast cancer patients [1]. It also seems to impact favorably risk of any disease recurrence and survival [2]. Conventionally, the number of involved axillary lymph nodes (LN) and the size of the primary tumor are considered, and postmastectomy radiotherapy is generally recommended for those with 3 or more involved axillary LN and/or those with large primary tumors (5 cm or greater) [3,4]. After mastectomy, loco-regional relapses are mainly located on the chest wall, followed by supraclavicular and axillary areas. The rate of clinical relapse in internal mammary lymph nodes (IMNs) is low [5] and the treatment of the IMNs remains debatable [6,7]. Published results of nonrandomized studies of the radiotherapy to the IMNs vary widely and controversy exists regarding the need to treat this region [8,9]. A recent meta-analysis of randomized EORTC 22922-10925, MA.20 and French trials showed that internal mammary and medial supraclavicular LN irradiation statistically significantly improve progression-free, distant metastasis free and overall survival in stage I–III breast cancer [10]. According to the results of the randomized trial from France, 2 dimensional techniques failed to demonstrate a survival benefit for IMN irradiation [11].

Radiotherapy for IMN involves some incidental exposure of the heart to ionizing radiation. Modern treatment planning and delivery techniques lead to more conformal dose distribution, but the long-term clinical outcomes of this treatment especially in terms of cardiac toxicity is recognized [11,12] and require further investigation. Minimizing radiation doses to the heart is a particularly important issue in breast cancer radiotherapy. Brachytherapy is widely applied in breast cancer treatment. One of its types – accelerated partial breast irradiation – is time-saving and it has cosmetic advantages and enables preservation of normal organs such as heart and lungs [13]. The use of accelerated partial breast irradiation brachytherapy is consistently increasing. In contrast, brachytherapy of the internal mammary chain nodal area is rare. Brachytherapy (a catheter placed into the internal mammary vessel) was performed at our center.

The aim of this study was to evaluate the efficacy of IMN RT in long-term clinical outcomes between different risk subgroups. We analyzed our institutional database on a large cohort of patients with central and medial breast cancer treated with IMN irradiation after radical mastectomy.

2. Materials and methods

2.1. Study design

We carried out a retrospective analysis of all patients treated with IMN radiotherapy after mastectomy for inner and central-located breast cancer between January 1987 and December 1997 in the Institute of Oncology, Vilnius University. We used the following criteria for the inclusion of the patients: histologically confirmed unilateral invasive carcinoma of the breast; T_{1-2}, N_{0-1}, M_0 disease (TNM classification 1997), no previous or concomitant malignant disease. A total of 588 patients received RT.

The RT fields used for the treatment of postoperative setting were designed to encompass the entire chest wall and regional lymphatics. A total of radiation doses of 50 Gy were delivered in 25 fractions of 2 Gy over 4 weeks to the chest wall. The supraclavicular fossa was treated with anterior photon field to 40–44 Gy. Anterior or two opposed photon fields to 38–40 Gy were applied to axillary LN. In addition, internal mammary node irradiation was applied to 320 patients (IMN RT group). A total of 268 patients did not receive postoperative IMNs irradiation and should be regarded as the non-IMN RT group. Two sub-groups of the IMN RT group were treated differently: 165 patients received external beam radiation therapy (IMN-EB subgroup) while Californium-252 (^{252}Cf) neutron source brachytherapy was applied to 155 patients (IMN-BT subgroup). ^{252}Cf neutron sources were indicated after mastectomy. On the first or second postoperative day, two flexible ^{252}Cf sources with active length of 60 mm and with total activity 5–15 μg of ^{252}Cf were inserted into the catheters. An empirical radio-biological model by Ryabukhin was used for the isoeffective doses (Gy_{eq}) of ^{252}Cf brachytherapy [14]. A relative biological effectiveness for late and early normal tissue damage (RBE) of 5.5–6.8 was used for calculating the equivalent dose. The irradiation dose at a distance of 1 cm from the center of the sources was in the range 34–40 Gy_{eq} (median 40 Gy_{eq}) with an exposure time of 42–96 h.

An adjuvant systemic chemotherapy or hormonal therapy was indicated in node-positive patients. Adjuvant tamoxifen was generally considered for postmenopausal, ER-positive PR-positive, or ER/PR-unknown patients with node positive or high-risk node-negative disease. Adjuvant treatment consisted of cyclic administration of CMF (cyclophosphamide; methotrexate; 5-fluorouracil) in 351 (60%) patients, FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) in 15 patients. Nine patients received Adriamycin (doxorubicin) and cyclophosphamide (AC); 219 patients (37%) received a 3–5 year tamoxifen therapy.

Patient characteristics at the time of initial diagnosis of breast cancer, stratified by the radiation treatment group are presented in Table 1. The following clinical data were included: age, tumor stage on the basis of pTNM classification, histologic tumor type, quadrant of tumor, axillary nodal status, RT, chemotherapy and hormonal therapy, date of recurrence (if occurred), location of recurrence, second primary cancer, date of distant metastases, date of breast cancer-associated death or nonbreast cancer-associated death. Clinical examination was repeated every 3 months during the first year, then every 6 months during the second through the tenth year, and annually thereafter for up to 25 years.

A complete follow-up until December 31, 2009, on vital status was obtained through linkage to the Causes of Death Register and the Residents' Register of Lithuania. Causes of death were confirmed by civil vital records kept at the Lithuanian State Historical Archives. Breast cancer was the cause of death if verified by autopsy or if recurrent disease had been diagnosed prior to death. Death from ischemic heart and other cardiovascular disease (CVD) was defined by the International Classification of Disease (ICD) 9th edition codes by 410–414 and ICD-10 codes by I_{20}–I_{25}. Follow-up time was

Table 1 – Patient demographic, clinicopathologic characteristics and comparisons between patients treated with and without IMN RT.

Characteristics	No IMN RT, *n* (%)	IMN-EB RT, *n* (%)	IMN-BT RT, *n* (%)	P
Patients, *n*	268	165	155	
Follow-up, years	8.0 (±5.4)	9.9 (±6.4)	9.4 (±5.9)	0.486
Age group, years				
≥40	27 (10.3)	23 (14.7)	14 (9.4)	
41–50	63 (24.0)	37 (23.7)	39 (26.2)	
51–60	85 (32.3)	52 (33.3)	37 (24.8)	
>60	88 (33.5)	44 (28.2)	59 (39.6)	0.252
Tumor size				
≤2 cm	59 (26.5)	51 (32.7)	31 (16.1)	
>2 cm	164 (73.5)	161 (83.9)	105 (67.3)	0.001
No. of positive sentinel LN				
0	106 (39.6)	70 (42.4)	105 (53.6)	
1–3	90 (33.6)	63 (38.2)	67 (34.2)	
≥4	72 (26.9)	24 (12.2)	32 (19.4)	0.001
Histological type				
Ductal	145 (54.1)	88 (53.3)	122 (78.7)	
Lobular	123 (45.9)	77 (46.7)	33 (21.3)	0.140
Risk group				
Low	7 (2.6)	10 (6.1)	7 (4.5)	
Moderate	134 (50.0)	103 (62.4)	113 (72.9)	
High	127 (47.4)	52 (31.5)	35 (22.6)	<0.001
Adjuvant systemic therapy				
Chemotherapy	172 (64.2)	106 (64.2)	125 (63.8)	0.995
Chemotherapy & hormonal	93 (34.7)	41 (24.8)	35 (17.9)	<0.001
Hormonal therapy	121 (45.1)	62 (37.6)	48 (24.5)	<0.001

IMN, internal mammary lymph node; EB, external beam irradiation; BT, brachytherapy; LN, lymph node.

defined as the time between initial diagnosis of breast cancer date and the date of the last checkup or death.

The study protocol and data handling procedures were approved by the Regional Biomedical Research Ethical Committee in Vilnius (September 3, 2008; No. 52).

2.2. *Statistical analysis*

Actuarial survival rates were measured from the end of radiotherapy and estimated using the Kaplan–Meier life-table method. The proportional hazards regression modeling was used to assess the impact of IMN radiotherapy on long-term clinical outcomes. The end-points for survival were loco/regional recurrence-free, distant metastasis-free survival, disease-free survival, cancer-specific survival, and all-cause mortality.

Loco/regional recurrence-free survival (LRRS) was defined as the first site of recurrence involving the chest wall (local) or/and ipsilateral axillary, supraclavicular and internal mammary chain LN. LRR concurrent with distant metastasis was recorded as LRR. The time until LRR was defined as the time interval between the date of diagnosis and the date on which the recurrence was objectified with an appropriate diagnostic test or the date of the last follow-up.

Events included in the analysis of disease-free survival (DFS) were first recurrence at a local, regional or distant site and death without evidence of cancer. DFS time after the radiation was defined as the interval from the date of diagnosis to LRR, distant metastases, ipsilateral breast cancer, contralateral breast cancer, death from breast cancer, whichever occurred first [15].

Event-free survival was defined as the interval from date of diagnosis until the date of the following first events: LRR or distant metastasis, second malignancy, including contralateral breast cancer, or death.

Secondary outcomes included breast cancer death, death from all-cause, and death from CVD. Time to these endpoints was defined as the time interval from the date of diagnosis to death from respectively causes or the last date of follow-up.

The probabilities of endpoints were calculated using the Cox method with adjustment for the covariates included in the multivariate analyses of HRs. These covariates included age at the time of initial therapy (<50, 50–60, >60), clinical tumor (T) category on the basis of TNM classification, and LN status (0, 1–3, ≥4). Initial treatment was entered into the model using three types of IMN RT (IMN-EB, IMN-BT, no IMN irradiation) and two separate binomial variables (yes vs. no) for chemotherapy and hormonal therapy.

Patients were categorized into three clinically relevant subgroups by risk status: low-risk patients (tumor [T] stage $T_{1–2}$ and/or node [N] stage N_0), moderate-risk patients (stage $T_{1–2}$ N_1) and high-risk patients (stage $T_{3–4}$ $N_{2–3}$) [16]. HRs for death from CVD with 95% confidence intervals were estimated using Cox proportional hazards regression models with attained age as the time scale. The models were adjusted for body mass index and chemotherapy. Kaplan–Meier curves were generated for CVD death-free survival at 10-year interval. The log-rank test was used to compare patients with and without IMN RT. For categorical variables the chi square test was used. A value of P <0.05 was considered statistically significant. All tests are two-sided. All statistical analyses were performed using SPSS 19.0 for Windows (IBM Corporation, Somers, NY, USA).

3. Results

Median duration of the follow-up of all patients was 8.5 years (range, 1.5–22.7 years). The median age of the 588 patients at diagnosis was 55 years (range, 30–79 years), and not significantly different between the 3 groups. The median tumor size was 3.0 cm (range, 0–10 cm), 355 patients (60.4%) had ductal carcinoma, and 233 patients (46.5%) had pathologically involved LN (Table 1). Overall, 24.5% of the cohort received adjuvant tamoxifen and 64% received adjuvant chemotherapy. In total, 24 patients (4.1%) were subclassified as low risk, 350 patients (59.5%) were classified as moderate risk, and 214 patients (36.4%) were classified as high risk. A total of 406 women (69.0%) died of any cause, yielding an actuarial 10-year overall survival rate of 44.5% (95% CI, 36%–48%). The 10-year actuarial survival was 50.4% for patients with moderate risk and 34.8% for high-risk patients.

3.1. *Recurrence at a local, regional or distant site*

There were 106 loco-regional recurrences that occurred prior to any other relapse or death. A total of 62 (58.5%) recurrences occurred in the chest wall. The 26 (24.4%) of subsequent recurrences following radiation were found in axillary LN and 30, in supraclavicular LN (28.3%). The rate of clinical relapse in internal mammary chain was low, i.e., approximately 2%. Twenty-six patients had multiple sites of recurrence after treatment. More than half (72 cases, 67.9%) of the eventual locoregional recurrence risk occurred during the first 5 years.

Table 2 summarizes the treatment effect for breast cancer recurrence according to type of event and according to IMN irradiation. The proportion changes in the rates of locoregional recurrence did not differ significantly according to whether or not IMN RT was given. A total of 282 (48.0%) patients developed distant metastasis. The 5- and 10-year distant recurrence-free survival rates were 51.9% (95% CI, 45.1%–58.7%) and 33.9% (95% CI, 27.0%–40.9%), respectively. Patients who had received either IMN-EB irradiation (HR, 0.69; 95% CI, 0.52–0.94, $P = 0.033$) or IMN-BT irradiation (HR, 0.76; 95% CI, 0.57–1.02, $P = 0.033$) had lower risk of distant metastases, compared with no IMN RT patients.

3.2. *Disease-free, cancer-specific and overall survival*

The 10-year actuarial DFS rates were 50% (95% CI, 43%–55%) for patients with moderate-risk and 34% (95% CI, 26%–42%) for patients with high-risk. There was no significant association between external beam IMN irradiation and DFS (HR, 0.83; 95% CI, 0.63–1.09, $P = 0.184$). DFS was also did not reach statistical significance in the patients having received IMN-BT with ^{252}Cf. Breast cancer was the cause of death for 53.3% of the patients treated with IMN-EB RT compared with 66.0% of the patients treated without IMN RT. The hazard of breast cancer-specific mortality decreased significantly in the patients receiving IMN-EB irradiation compared with not receiving IMN irradiation (HR, 0.76; 95% CI, 0.58–0.98; $P = 0.037$). The relative risk of death from any cause was significantly lower in patients undergoing IMN-EB RT. HR (95% CI) for IMN-EB RT was 0.73 (0.57–0.93) ($P = 0.011$).

Table 2 – Variation of treatment effect according to type of event and according to IMN[a] irradiation for the 588 patients.

Variable	No IMN irradiation	IMN-EB	IMN-BT
No. of patients	268	165	155
Locoregional recurrence (LRR)			
Cases	46	28	32
Relative risk[b] (95% CI)	1.00	0.98 (0.60–1.59)	1.60 (0.97–2.65)
P		0.929	0.067
Distant metastasis-free (DMF)			
Cases	142	84	68
Relative risk[b] (95% CI)	1.00	0.69 (0.52–0.94)	0.76 (0.57–1.02)
P		0.033	0.020
Disease-free survival (DFS)			
Cases	153	77	79
Relative risk[b] (95% CI)	1.00	0.83 (0.63–1.09)	1.02 (0.76–1.36)
P		0.184	0.910
Breast cancer-specific survival			
Cases	177	88	98
Relative risk[b] (95% CI)	1.00	0.76 (0.58–0.98)	0.94 (0.72–1.24)
P		0.037	0.672
All-cause mortality			
Cases	206	102	109
Relative risk[b] (95% CI)	1.00	0.73 (0.57–0.93)	0.84 (0.65–1.08)
P		0.011	0.163

[a] IMN, internal mammary lymph node; EB, external beam irradiation; BT, brachytherapy.
[b] Adjusted for age, tumor stage (1, 2, 3–4), N (0, 1–3, ≥4), tamoxifen (yes, no), chemotherapy (yes, no).

Table 3 – Multivariate analyses[a] of overall hazard ratio for probabilities of event, death from breast cancer and death from any cause stratified by IMN radiation and risk group.

Variable	Event-free survival		Death from breast cancer		Death from any cause	
	HR[c] (95% CI)	P	HR[c] (95% CI)	P	HR[c] (95% CI)	P
Moderate-risk subgroup[a] (n = 350)						
IMN-EB vs. no	0.67 (0.46–0.99)	0.043	0.64 (0.45–0.91)	0.013	0.75 (0.55–1.01)	0.060
IMN-BT vs. no	0.84 (0.58–1.21)	0.352	0.80 (0.57–1.11)	0.182	0.61 (0.44–0.83)	0.002
High-risk subgroup[b] (n = 214)						
IMN-EB vs. no	0.98 (0.65–1.49)	0.925	1.09 (0.70–1.68)	0.705	1.01 (0.66–1.55)	0.960
IMN-BT vs. no	1.20 (0.73–1.96)	0.464	0.77 (0.51–1.16)	0.211	0.81 (0.56–1.20)	0.288

[a] Moderate-risk stage T_{1-2} N_1.
[b] High-risk stage T_{3-4} N_{2-3}.
[c] Adjusted for age (<50, ≥50 years), tamoxifen therapy (yes, no), chemotherapy (yes, no).

3.3. *Multivariate analysis according to risk subgroup*

Results of multivariate analyses a of hazard ratio for probabilities of event, death from breast cancer and death from any cause stratified by IMN radiation and risk subgroup are presented in Table 3. Because of small number, patients with the low-risk of disease were excluded from further analysis.

Event-free survival is calculated when a particular treatment is given that is directed not toward improving survival, but to prevent or delay specific complications of the disease. In comparison to no IMN RT, IMN-EB RT resulted event-free survival (HR, 0.67; 95% CI, 0.46–0.91; P = 0.043) in patients with moderate-risk. In these patients, IMN RT was associated with a significant improvement of death from breast cancer-free survival (HR, 0.64; 95% CI, 45–0.91; P = 0.013). On multivariate analysis of patients with moderate-risk disease treated with IMN-BT RT was the only strong associated with overall survival. HR for death from all causes was 0.73 (95% CI, 0.57–0.93; P = 0.011). In contrast, there was no association between IMN RT and outcome of patients with high-risk disease in any of the study end points.

3.4. *Long-term side effects*

In total, 220 patients (39.1%) had side-effects related to breast cancer therapy: lung fibrosis, pneumonitis, edema arm, evidence of coronary artery disease. Arm edema occurred in 92 (23.7%) of the 388 patients treated with radiation therapy and chemotherapy, compared with 29 (16.6%) of the 175 patients treated with radiotherapy alone (P = 0.035). Lung fibrosis was seen in 19 (10.9%) patients treated with radiation therapy and in 50 (12.9%) patients in the chemotherapy and radiation group (P = 0.036). The rate of cardiovascular disease was 25.9% among patients treated with radiation therapy and chemotherapy (35 of 388 patients) compared with 6.9% patients in the radiotherapy alone group (12 of 175 patients; P = 0.024). There were 16 deaths (2.7%) from CVD. After adjustment for chemotherapy and tamoxifen therapy, IMN irradiation was not significantly associated with risk of CVD mortality (data not shown). There were no increased rates of cardiac disease among patients who received IMN-EB radiotherapy (HR, 95% CI, 0.35–3.51; P = 0.860) and IMN-BT (HR, 0.70; 95% CI, 0.20–2.44; P = 0.547).

4. Discussion

This study confirms the beneficial impact of external beam IMN RT on breast cancer-specific and overall survival. Our study provides evidence that post-mastectomy IMN-EB radiotherapy can improve event-free survival and breast cancer survival in moderate-risk subgroup of patients.

The results are in general agreement with recent meta-analysis supported benefits of IMN RT [10]. Recent randomized studies also showed a survival benefit for breast cancer patients who received systemic chemotherapy and postmastectomy IMN radiotherapy [11]. The overall survival benefits associated with radiation therapy increased with follow-up to 20 years compared with the trial results after 15 years of follow-up [17].

Considerable discussion regarding the need for delivery of radiotherapy to the internal mammary lymph nodes continues. There is no consensus over which group of patients could benefit from IMN radiotherapy and what kind of IMN radiotherapy should be applied. Our study suggests that patients of the moderate-risk subgroup are the most likely to reach better overall and progression-free survival rates when treated with IMN radiotherapy. However, it is still not a standard way of treatment at our institution. Current studies that are still ongoing as well as future investigations should bring more clarity to the issue.

The IMNs have been generally recognized as potential sites of regional breast cancer spread. Treatment guidelines stipulate that IMN irradiation must be applied to clinically or pathologically positive nodes. According to Eubank et al., FDG-PET-CT scans at the time of the clinical appearance of distant metastasis have shown high rates of unsuspected mediastinal lymph node involvement that may have originated in the internal mammary lymph node as source of further dissemination [18]. Another hypothesis compatible with the observations is that micrometastasis in the internal mammary lymph node represent a source for metastatic spread without growing to clinically detectable size before distant metastases have been diagnosed improving the DFS and OS rates.

Different irradiation treatment techniques have been proposed, including electron beam therapy. A novel HDR brachytherapy technique for IMN irradiation seems to be promising in combination with IMN-EB irradiation [19].

Creation of an artificial space between the target and risk organs in a minimally invasive procedure may provide an effective solution [13,20].

It is necessary to balance the costs, risks and benefits of sophisticated treatment modalities. The proximity of this region to the heart and lungs raises deep concerns about potential treatment related toxicities. Radiotherapy of the IMN undoubtedly increases the dose to the heart regardless of the radiation technique applied.

Brachytherapy with ^{252}Cf causes rapid dose fall-off at a few centimeters around the implant. This allowed the irradiation of parasternal lymph-nodes in shortest time with simultaneous substantial decrease of radiation exposure of heart, lung, and mediastinal organs, and of spinal marrow [14], but treatment with this approach has some limitations [21] and is exceedingly rare.

In our 10-year follow-up, there were no significant cardiac or lung toxicities related to radiation therapy. Radiotherapy of the IMN was not associated with an excess of cardiac death or cardiac toxicity rate in any of the three trials discussed in recent a randomized trial [11].

Our study had several limitations. First, it has inherent selective biases in patient selection and treatment assignment because of the retrospective nature of the design. We endeavored to mitigate several risk variables by controlling for them in a multivariate model. It is possible that other unmeasured confounders that we did not take into account may have influenced, in part, our current results. There were additional confounding factors that we did not consider, e.g., the use of diabetes medications, smoking status, history of cardiovascular, etc. The dose of radiation to the heart could not be determined from the data available. Despite these limitations, our study provides evidence supporting the clinically beneficial long-term effect of IMN RT in patients with the breast cancer.

5. Conclusions

Long-term follow-up shows sustained benefit in event-free survival and cancer specific survival of postmastectomy external beam radiotherapy the internal mammary lymph node for patients with moderate-risk breast cancer.

Conflict of interest

The authors state no conflict of interest.

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