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Effect of Elective Internal Mammary Node Irradiation on Disease-Free Survival in Women With Node-Positive Breast Cancer
A Randomized Phase 3 Clinical Trial

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IMPORTANCE The benefit of internal mammary node irradiation (IMNI) for treatment outcomes in node-positive breast cancer is unknown.

OBJECTIVE To investigate whether the inclusion of IMNI in regional nodal irradiation improves disease-free survival (DFS) in women with node-positive breast cancer.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, phase 3 randomized clinical trial was conducted from June 1, 2008, to February 29, 2020, at 13 hospitals in South Korea. Women with pathologically confirmed, node-positive breast cancer after breast-conservation surgery or mastectomy with axillary lymph node dissection were eligible and enrolled between November 19, 2008, and January 14, 2013. Patients with distant metastasis and those who had received neoadjuvant treatment were excluded. Data analyses were performed according to the intention-to-treat principle.

INTERVENTIONS All patients underwent regional nodal irradiation along with breast or chest wall irradiation. They were randomized 1:1 to receive radiotherapy either with IMNI or without IMNI.

MAIN OUTCOMES AND MEASURES The primary end point was the 7-year DFS. Secondary end points included the rates of overall survival, breast cancer–specific survival, and toxic effects.

RESULTS A total of 735 women (mean [SD] age, 49.0 [9.1] years) were included in the analyses, of whom 373 received regional nodal irradiation without IMNI and 362 received regional nodal irradiation with IMNI. Nearly all patients underwent taxane-based adjuvant systemic treatment. The median (IQR) follow-up was 100.4 (89.7-112.1) months. The 7-year DFS rates did not significantly differ between the groups treated without IMNI and with IMNI (81.9% vs 85.3%; hazard ratio [HR], 0.80; 95% CI, 0.57-1.14; log-rank $P = .22$). However, an ad hoc subgroup analysis showed significantly higher DFS rates with IMNI among patients with mediocentrally located tumors. In this subgroup, the 7-year DFS rates were 81.6% without IMNI vs 91.8% with IMNI (HR, 0.42; 95% CI, 0.22-0.82; log-rank $P = .008$), and the 7-year breast cancer mortality rates were 10.2% without IMNI vs 4.9% with IMNI (HR, 0.41; 95% CI, 0.17-0.99; log-rank $P = .04$). No differences were found between the 2 groups in the incidence of adverse effects, including cardiac toxic effects and radiation pneumonitis.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that including IMNI in regional nodal irradiation did not significantly improve the DFS in patients with node-positive breast cancer. However, patients with medially or centrally located tumors may benefit from the use of IMNI.

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Visual Abstract

Supplemental content

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Internal mammary node irradiation (IMNI) has been a subject of controversy since radiotherapy to the chest wall or breast and regional lymph nodes was shown to improve survival in patients with early-stage breast cancer.[1-5] Two large phase 3 randomized clinical trials, NCIC-CTG (National Cancer Institute of Canada Clinical Trials Group) MA.20 and EORTC (European Organisation for Research and Treatment of Cancer) 22922/10925, demonstrated the disease-free survival (DFS) benefit associated with regional nodal irradiation when added to whole-breast or chest wall irradiation after surgery in node-positive breast cancer or high-risk node-negative breast cancer.[6,7] Recently, long-term follow-up data from the EORTC 22922/10925 trial showed that regional nodal irradiation resulted in a substantial reduction in breast cancer mortality and recurrence.[8] In both trials, irradiation was directed at the internal mammary and supraclavicular nodes, with or without undissected level 2 to 3 lymph nodes. Because all regional lymphatics were targeted, it is not clear which part of the regional nodal irradiation contributed to the improvement in treatment outcome. A Danish population-based study (DBCG-IMN [Danish Breast Cancer Cooperative Group-Internal Mammary Node]) and a French phase 3 randomized clinical trial examined the sole benefit of IMNI; however, their results were contradictory.[9,10] The DBCG-IMN study supported the inclusion of IMNI, whereas the French trial did not report a survival benefit. Moreover, those studies included patients who were treated when taxane and anti-*ERBB2* (formerly *HER2*) drugs were not yet introduced as standard adjuvant systemic therapy.[11,12] Thus, it is unknown whether IMNI has clinical benefit in the contemporary treatment of breast cancer, and there is marked discrepancy in the use of this treatment worldwide.[13,14]

In some treatment centers, IMNI is used in patients with a high risk of recurrence, whereas only the axillary and medial supraclavicular lymph nodes are irradiated in other centers. The criteria for consideration of IMNI and the percentage of patients who actually receive it vary between countries. In these circumstances, the decision to treat the IMNs is challenging for radiation oncologists. The barriers to its application include the added risk of potential cardiac and pulmonary toxic effects with larger irradiated volumes, increased complexity of the radiotherapy plan, and low rates of detectable solitary recurrences in the internal mammary region.[15-19]

Because of the uncertainties of the role of IMNI, the Korean Radiation Oncology Group initiated a multicenter, phase 3 randomized clinical trial (KROG 08-06 study) to investigate the effect of elective IMNI on DFS in regional nodal irradiation that was added to breast or chest wall irradiation in women with node-positive breast cancer. The results of this trial are presented here.

Key Points

Question Does internal mammary node irradiation (IMNI) improve disease-free survival in patients with node-positive breast cancer?

Findings In this randomized clinical trial of 735 women with node-positive breast cancer, 7-year disease-free survival did not significantly differ between those who were randomized to receive regional nodal irradiation with IMNI and those who were randomized to receive regional nodal irradiation without IMNI. However, in a subgroup analysis of patients with mediocentrally located tumors, the 7-year disease-free survival rate was improved by 10% in the IMNI group.

Meaning While this randomized clinical trial found no difference in 7-year disease-free survival between the the IMNI and no IMNI groups, the findings of an unprespecified subgroup analysis suggest that including IMNI in regional nodal irradiation might be considered for patients with medially or centrally located tumors.

Methods

Study Design and Patients

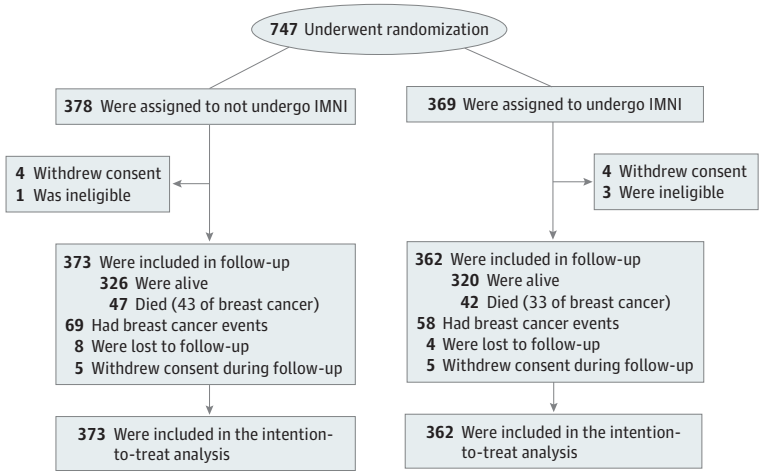
This multicenter, prospective, phase 3 randomized clinical trial was conducted from June 1, 2008, to February 29, 2020, at 13 hospitals in South Korea (Yonsei Cancer Center, Seoul; Proton Therapy Center, National Cancer Center, Goyang; Chonnam National University Hwasun Hospital, Hwasun; Dong-A University Hospital, Busan; Samsung Medical Center, Seoul; Asan Medical Center, Seoul; Dongsan Medical Center, Daegu; Gachon University Gil Medical Center, Incheon; Gangnam Severance Hospital, Seoul; Pusan National University School of Medicine, Busan; Bundang CHA Medical Center, Seongnam; Ewha Womans University School of Medicine, Seoul; and Inha University College of Medicine, Incheon). The trial protocol (Supplement 1) was approved by the institutional review board at each participating hospital. Written informed consent was obtained from patients before randomization. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Eligible patients were women with histologically confirmed, node-positive breast cancer who had undergone a modified radical mastectomy (MRM) or breast-conserving surgery (BCS) and an axillary dissection with removal of 8 or more nodes. Patients were excluded if they had received neoadjuvant chemotherapy, had bilateral breast cancer or distant metastasis, or had a history of other malignant neoplasms. Patients with evidence of involvement of the supraclavicular nodes or IMNs at diagnosis were also excluded. Potentially eligible patients were advised to undergo chest computed tomography (CT), chest radiography, abdominal ultrasonography, bone scan, and/or positron emission tomography for accurate staging.

Randomization, Masking, and Treatment Regimens

Randomization was performed by personnel at the Korean Radiation Oncology Group headquarters at the National Cancer Center in Goyang, South Korea. First, patients were stratified according to the N category (N1 vs N2 or N3) and surgery type (BCS vs MRM). Second, patients were randomized 1:1 to receive radiotherapy either with or without IMNI using the method of permuted block randomization with mixed block sizes of 2 and 4. The trial enrolled 747 patients between November 19, 2008, and January 14, 2013. Of these patients, 735 were included in the intention-to-treat analysis, and 378 were

Figure 1. CONSORT Flow Diagram



IMNI indicates internal mammary node irradiation.

randomized to treatment without IMNI and 369 were randomized to treatment with IMNI (**Figure 1**).

Compared with patients who were treated without IMNI, those in the IMNI group underwent irradiation of the ipsilateral IMNs in the upper 3 intercostal spaces. Treatment randomization was not masked to clinicians or patients because of the nature of the intervention.

All patients received supraclavicular irradiation as routinely performed for node-positive disease, as well as breast or chest wall irradiation as appropriate. All patients also underwent CT-based simulation, and structures were manually contoured on CT scan slices. The radiotherapy techniques were determined at the discretion of the physician. Guidelines for radiotherapy, including the reverse hockey stick, standard tangent, partial wide tangent, and photon-electron combination techniques, are described in the trial protocol.[20] Radiation was administered once per day at a dose of 1.8 to 2 Gy up to a total dose of 45 to 50.4 Gy. A sequential tumor bed boost to the conserved breast was allowed.

Follow-up and Outcomes

Patients were reevaluated at 1 month after radiotherapy, every 6 months for the first 3 years, and then every year unless the disease recurred or the patient died. Acute adverse events were recorded during and at the end of radiotherapy, and late adverse events were recorded annually after the completion of radiotherapy according to the toxic effect criteria of the RTOG (Radiation Therapy Oncology Group)/EORTC. To assess radiation pneumonitis, we compared chest radiographs that were obtained before radiotherapy with those that were obtained within 6 months after treatment. Symptoms, such as cough, dyspnea, and the incidence of steroid treatment, were also identified. The tumor location was determined using the findings on ultrasonography. Tumors were considered mediocentrally located when their epicenters were located in the inner quadrants of the breasts or at the 12- or 6-o'clock position. A patient with multiple tumors was considered to have the mediocentrally located tumor if any one of the tumors was located in this area.

The primary end point was the 7-year DFS. The secondary end points were the rates of overall survival, breast cancer mortality, local recurrence, regional recurrence, distant metastasis-free survival (DMFS), and acute and late adverse events. Disease-free survival was calculated from the time of randomization to the first recurrence in the ipsilateral breast or chest wall, the regional nodal area, or a distant site or to death from breast cancer. Overall survival and breast cancer mortality were defined as the time from randomization to death from any cause and from randomization to death from breast cancer, respectively. Time to local recurrence, time to regional recurrence, and DMFS were calculated from the time of randomization to the first recurrence in the ipsilateral breast or chest wall, the regional nodal area, and a distant site, respectively.

Statistical Analysis

The trial was designed to detect a difference of 10 percentage points (70% with IMNI vs 60% without IMNI) in the 7-year DFS with breast or chest wall irradiation combined with regional nodal irradiation, including IMNI vs excluding IMNI (hazard ratio [HR] for death, 0.70).[21] We estimated that 747 patients would be needed to give the study 80% power at a 2-sided significance level of 5% to detect a 10 percentage-point difference as assessed by means of the log-rank test.

Time-to-event curves were estimated with the Kaplan-Meier method. Stratified log-rank tests, which were adjusted for the stratification factors excluding the treatment center, were used to compare the study groups. Cox proportional hazards regression models, which were adjusted for the same stratification factors, were used to estimate the relative treatment effects. We also conducted a post hoc sensitivity analysis for time-to-event curves using the cumulative incidence function and Gray test for competing risks for the between-group comparison. Data on patients who were randomized were analyzed according to the intention-to-treat principle.

A 2-sided $P < .05$ was used to indicate statistical significance, with no adjustment for multiple testing. Analyses were performed from March 6, 2020, to February 21, 2021, using IBM

SPSS Statistics, version 25 (IBM Corp) and R, version 4.0.3 (R Foundation for Statistical Computing).

Results

Patient and Tumor Characteristics

A total of 735 patients, of whom 373 were in the without-IMNI group and 362 in the with-IMNI group, were included in the follow-up and intention-to-treat analysis (Figure 1). The median (IQR) follow-up at the time of this analysis was 100.4 (89.7-112.1) months.

The characteristics of the patients at baseline were similar in the 2 study groups (**Table 1**). The mean (SD) age was 49.0 (9.1) years. Most patients had tumors that were categorized as either T1 (230 [31.3%]) or T2 (412 [56.1%]). The tumor locations were medial or central in 306 patients (41.6%) and lateral in 428 patients (58.2%). The nodal stage was N1 in 304 patients (41.4%), N2 in 269 (36.6%), and N3 in 162 (22.0%). Most patients had estrogen receptor–positive (524 [71.3%]) and/or progesterone receptor–positive (459 [62.4%]) disease. About half of the patients underwent BCS (367 [49.9%]), and the other half underwent MRM (368 [50.1%]). Most patients received combination chemotherapy (727 [98.9%]) with a taxane-containing regimen (703 [95.6%]), along with endocrine therapy (494 [67.2%]). Of the 171 patients with *ERBB2*-positive breast cancer (3+ overexpression), 132 (77.2%) received *ERBB2*-targeted therapy. The median prescribed radiation dose to the treated area was 50.4 Gy, with a fractional dose of 1.8 Gy. Boost irradiation was used in most patients who underwent BCS (358 of 367 patients [97.5%]). Treatment interruption for more than 1 week was rare (8 [1.1%]). The radiation techniques are shown in eTable 1 in Supplement 2.

Outcomes

Overall, 47 patients (12.6%) in the group treated without IMNI and 42 patients (11.6%) in the IMNI group died. In both groups, the main cause of death was breast cancer (without IMNI: 43 patients [11.5%]; with IMNI: 33 patients [9.1%]) (eTable 2 in Supplement 2). Deaths from other causes were more frequent in the group treated with vs without IMNI (9 [2.5%] vs 4 [1.1%]).

Disease recurrence occurred in 69 patients (18.5%) in the group without IMNI and 58 patients (16.0%) in the group with IMNI (eTable 3 in Supplement 2). The first recurrence was distant metastasis, with or without other types of recurrence, in 61 patients (16.4%) in the group treated without IMNI and 50 patients (13.8%) in the IMNI group. Regional recurrence, with or without other types of recurrence, occurred in 16 patients (4.3%) in the group without IMNI and 8 patients (2.2%) in the IMNI groups. The first recurrence involved IMN recurrence in 8 patients (2.1%) in the group treated without IMNI and 3 patients (0.8%) in the IMNI group.

Compared with the group who did not receive IMNI, the IMNI group showed a 3.4% improvement in the 7-year DFS rates, but this improvement was not statistically significant (81.9% vs 85.3%; HR, 0.80; 95% CI, 0.57-1.14; log-rank P = .22) (**Figure 2**). In the without-IMNI vs with-IMNI groups, the 7-year breast cancer mortality rates were 10.8% vs 8.4% (HR, 0.74; 95% CI, 0.47-1.16; log-rank P = .19), the 7-year DMFS rates were 83.2% vs 85.8% (HR, 0.81; 95% CI, 0.56-1.16; log-rank P = .25), and the 7-year overall survival rates were 88.2% vs 89.4% (HR, 0.87; 95% CI, 0.57-1.31; log-rank P = .50). Similar patterns were observed in the sensitivity analysis for survival outcomes after adjustment for competing risks (eFigures 1-5 in Supplement 2).

In a subgroup analysis, a pattern of longer DFS with IMNI was observed in the subgroups of MRM; removal of fewer than 10 nodes; estrogen receptor– and progesterone receptor–negative disease; and T1, T3 or T4, N1, N2, and grade 3 diseases, but the pattern was not statistically significant (**Figure 3**). In addition, DFS was significantly improved only in patients with mediocentrally located tumors compared with patients with tumors in the lateral location (HR, 1.05; 95% CI, 0.69-1.62; log-rank P = .81) (eFigure 6 in Supplement 2). A significant interaction (P = .03) was found between the treatment effect and tumor location. In the analysis by tumor locations, 7-year DFS was significantly improved in the IMNI group; the DFS at 7 years was 81.6% without IMNI and 91.8% with IMNI (HR, 0.42; 95% CI, 0.22-0.82; log-rank P = .008) among patients with mediocentrally located tumors (eFigure 7 in Supplement 2). The breast cancer mortality at 7 years was not significantly different between the groups among patients with laterally located tumors (HR, 0.91; 95% CI, 0.53-1.57; log-rank P = .74) (eFigure 8 in Supplement 2). The breast cancer mortality at 7 years was 10.2% without IMNI and 4.9% with IMNI (HR, 0.41; 95% CI, 0.17-0.99; log-rank P = .04) (eFigure 9 in Supplement 2), and the DMFS at 7 years was 82.3% without IMNI and 91.8% with IMNI (HR, 0.44; 95% CI, 0.23-0.85; log-rank P = .01) among patients with mediocentrally located tumors (eTable 4 in Supplement 2). The improvements in DFS, breast cancer mortality, and DMFS with IMNI in a subgroup of patients with mediocentrally located tumors were also observed when the 2 groups were compared by competing risks analyses (eFigures 10-12 in Supplement 2). The overall survival at 7 years was 88.5% without IMNI and 93.2% (HR, 0.51; 95% CI, 0.24-1.11; log-rank P = .08) among patients with mediocentrally located tumors (eFigure 13 in Supplement 2). The analysis of pattern of failure showed that IMNI vs no IMNI more prominently reduced the occurrence of distant metastasis (crude rate: 6.5% vs 16.3%) in patients with mediocentrally located tumors (eTable 5 in Supplement 2). In patients with mediocentrally located tumors, all characteristics were well balanced between the groups (eTable 6 in Supplement 2).

Adverse Events

No differences in the toxic effect rates were found between the groups treated with IMNI or without IMNI, including arm edema (24.0% vs 22.3%), brachial plexopathy (0.8% vs 0.5%), rib fracture (1.1% vs 0.3%), skin reaction (17.7% vs 18.2%), soft-tissue fibrosis and necrosis (1.4% vs 1.3%), and cardiac problems (2.2% vs 1.3%) (**Table 2**). There was a high rate of radiation pneumonitis in the IMNI group, but the difference was not statistically significant (6.1% vs 3.2%; P = .06). This finding may be attributable to the substantially higher median (range) value of mean ipsilateral lung dose of 17.8 (5.7-37.1) Gy in patients

Table 1. Patient Characteristics

Characteristic	No. (%)		
	All patients (n = 735)	Treated without IMNI (n = 373)	Treated with IMNI (n = 362)
Age, median (range), y	48 (28-77)	48 (31-74)	48 (28-77)
Laterality			
Right	367 (49.9)	186 (49.9)	181 (50.0)
Left	368 (50.1)	187 (50.1)	171 (50.0)
Tumor location			
Lateral	428 (58.2)	220 (59.0)	208 (57.5)
Medial or central	306 (41.6)	153 (41.0)	153 (42.3)
Unknown	1 (0.1)	0	1 (0.3)
Histologic type			
Ductal	673 (91.6)	352 (94.4)	321 (88.7)
Lobular	25 (3.4)	9 (2.4)	16 (4.4)
Mixed ductal and lobular	5 (0.7)	2 (0.5)	3 (0.8)
Other	32 (4.4)	10 (2.7)	22 (6.1)
T category			
T1	230 (31.3)	111 (29.8)	119 (32.9)
T2	412 (56.1)	218 (58.4)	194 (53.6)
T3	87 (11.8)	41 (11)	46 (12.7)
T4	6 (0.8)	3 (0.8)	3 (0.8)
N category			
N1	304 (41.4)	157 (42.1)	147 (40.6)
N2	269 (36.6)	136 (36.5)	133 (36.7)
N3	162 (22.0)	80 (21.4)	82 (22.7)
Tumor size, median (range), cm	2.5 (0-11)	2.5 (0-9)	2.5 (0.2-11)
No. of dissected nodes, median (range)	17 (4-53)	17 (8-53)	18 (4-47)
No. of positive nodes, median (range)	4 (1-48)	4 (1-48)	5 (1-36)
Histologic grade			
1	90 (12.2)	44 (11.8)	46 (12.7)
2	292 (39.7)	144 (38.6)	148 (40.9)
3	324 (44.1)	173 (46.4)	151 (41.7)
Unknown	29 (3.9)	12 (3.2)	17 (4.7)
Nuclear grade			
1	44 (6.0)	21 (5.6)	23 (6.4)
2	311 (42.3)	151 (40.5)	160 (44.2)
3	320 (43.5)	173 (46.4)	147 (40.6)
Unknown	60 (8.2)	28 (7.5)	32 (8.8)
Estrogen receptor			
Negative	203 (27.6)	116 (31.1)	87 (24)
Positive	524 (71.3)	254 (68.1)	270 (74.6)
Unknown	8 (1.1)	3 (0.8)	5 (1.4)
Progesterone receptor			
Negative	269 (36.6)	154 (41.3)	115 (31.8)
Positive	459 (62.4)	217 (58.2)	242 (66.9)
Unknown	7 (1.0)	2 (0.5)	5 (1.4)
p53 Sequence variant			
Negative	378 (51.4)	184 (49.3)	194 (53.6)
Positive	235 (32.0)	126 (33.8)	109 (30.1)
Unknown	122 (16.6)	63 (16.9)	59 (16.3)
ERBB2 (formerly *HER2*) status			
0	4 (0.5)	1 (0.3)	3 (0.8)
1	408 (55.5)	208 (55.8)	200 (55.2)
2	134 (18.2)	64 (17.2)	70 (19.3)
3	171 (23.3)	92 (24.7)	79 (21.8)
Unknown	18 (2.4)	8 (2.1)	10 (2.8)

(continued)

Table 1. Patient Characteristics (continued)

Characteristic	No. (%)		
	All patients (n = 735)	Treated without IMNI (n = 373)	Treated with IMNI (n = 362)
Perinodal extension			
Yes	269 (36.6)	128 (34.3)	141 (39.0)
No	367 (49.9)	193 (51.7)	174 (48.1)
Unknown	99 (13.5)	52 (13.9)	47 (13)
Lymphovascular invasion			
Yes	297 (40.4)	158 (42.4)	139 (38.4)
No	398 (54.1)	194 (52.0)	204 (56.4)
Unknown	40 (5.4)	21 (5.6)	19 (5.2)
Resection margin			
Negative	728 (99.0)	368 (98.7)	360 (99.4)
Positive	7 (1.0)	5 (1.3)	2 (0.6)
Surgery type			
Breast-conserving surgery	367 (49.9)	187 (50.1)	180 (49.7)
Modified radical mastectomy	368 (50.1)	186 (49.9)	182 (50.3)
IMN biopsy			
Yes	4 (0.5)	3 (0.8)	1 (0.3)
No	624 (84.9)	312 (83.6)	312 (86.2)
Unknown	107 (14.6)	58 (15.5)	49 (13.5)
Chemotherapy			
Taxane-containing regimen	703 (95.6)	360 (96.5)	343 (94.8)
Non-taxane-containing regimen	24 (3.3)	10 (2.7)	14 (3.9)
No	8 (1.1)	3 (0.8)	5 (1.4)
Hormonal therapy			
Yes	494 (67.2)	238 (63.8)	256 (70.7)
No	240 (32.7)	135 (36.2)	105 (29.0)
Unknown	1 (0.1)	0	1 (0.3)
ERBB2-targeted therapy			
Yes	163 (22.2)	83 (22.3)	80 (22.1)
No	571 (77.7)	290 (77.7)	281 (77.6)
Unknown	1 (0.1)	0	1 (0.3)

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

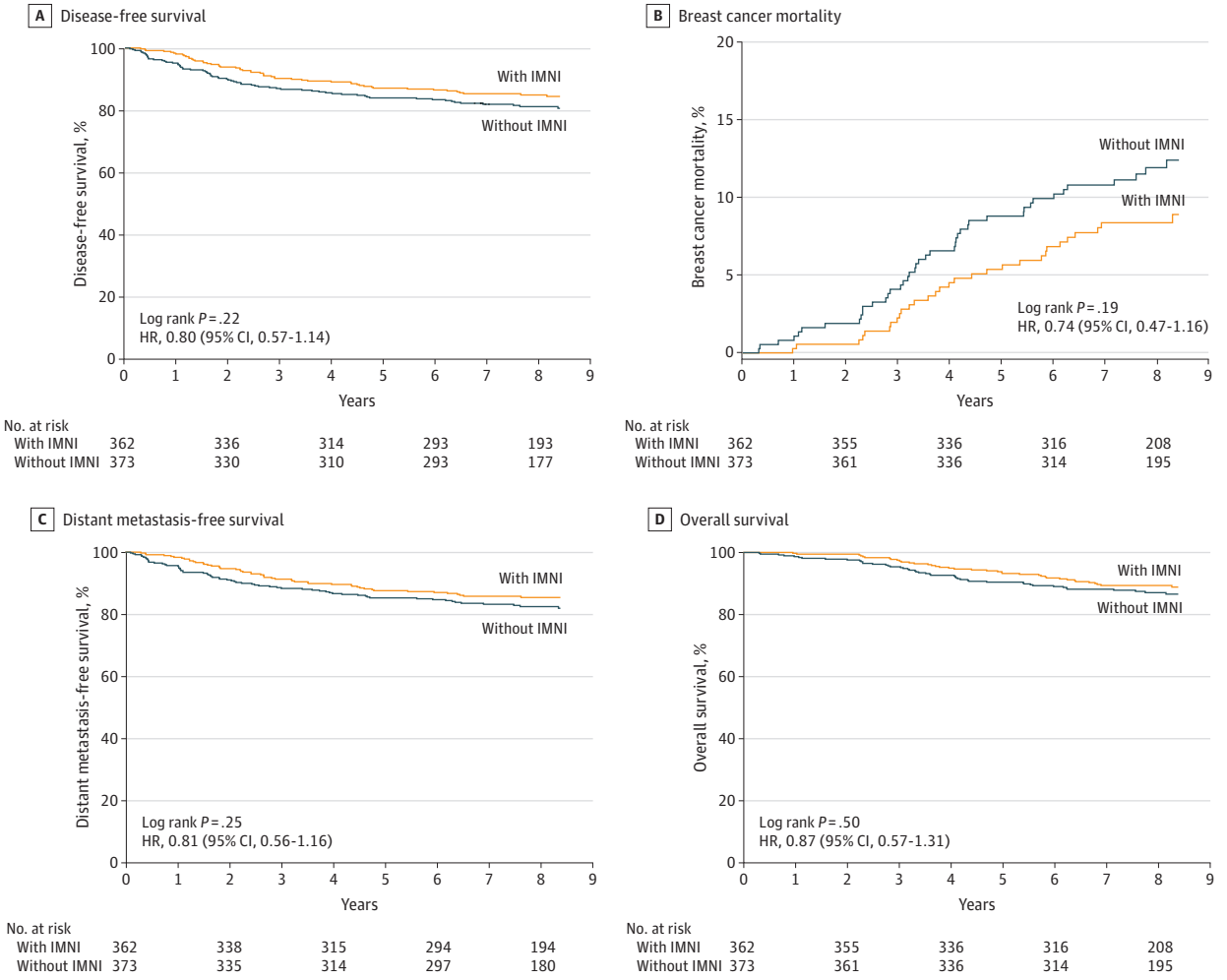
who were treated with IMNI vs 13.6 (0.4-28.2) Gy in patients who were treated without IMNI as well as higher median (range) lung V10 to V40 values (eg, V10: 43.8% [10%-85%] vs 30.9% [0.2%-77.6%]; $P < .001$) (eTable 7 in Supplement 2). However, the higher lung dose in the group treated with IMNI did not lead to an increased rate of serious radiation pneumonitis; no grade 3 or higher radiation pneumonitis was observed in either group.

Discussion

Internal mammary node irradiation has clinical significance for eradicating tumor cells in the IMN area, which can lead to distant and regional disease control. The effectiveness of IMNI is controversial, particularly in patients with medially located tumors or positive axillary nodes, because the chance of microscopic disease involvement is high.[22] The hesitation regarding delivering IMNI has several explanations. First, the absolute incidence of IMN recurrence is low, approximately 1%.[23] Second, IMNI leads to higher lung and heart doses with a larger irradiation volume, which may increase the risks for cardiac or pulmonary toxic effects.[18] Third, advancements in systemic drugs for breast cancer treatment enhance locoregional disease control, which may reduce the benefit of IMNI.[11,12]

In this trial, no significant benefit in DFS could be demonstrated for IMNI in patients with node-positive breast cancer who were treated with contemporary systemic radiation therapy. The absolute 7-year DFS benefit of 3.4% with IMNI was similar to the results of regional nodal irradiation in the NCIC-CTG MA.20, EORTC 22922/10925, and French randomized clinical trials (eTable 8 in Supplement 2).[6,7,10] The 7-year breast cancer–specific survival, DMFS, and regional recurrence rates also improved by approximately 3% in the IMNI group, but these differences were not statistically significant. The present study was designed to detect a difference of 10 percentage points (70% vs 60%) in the 7-year DFS. This assumption was based on a Korean retrospective study that found a 10-year DFS of 65% with IMNI and 57% without IMNI.[21] It seems that our hypothesis was overestimated for several reasons. The survival outcome was improved with the introduction of more systemic therapy, such as taxane and trastuzumab, and migration to an earlier stage, which may be attributed to the early

Figure 2. Disease-Free Survival, Breast Cancer Mortality, Distant Metastasis-Free Survival, and Overall Survival in All Patients



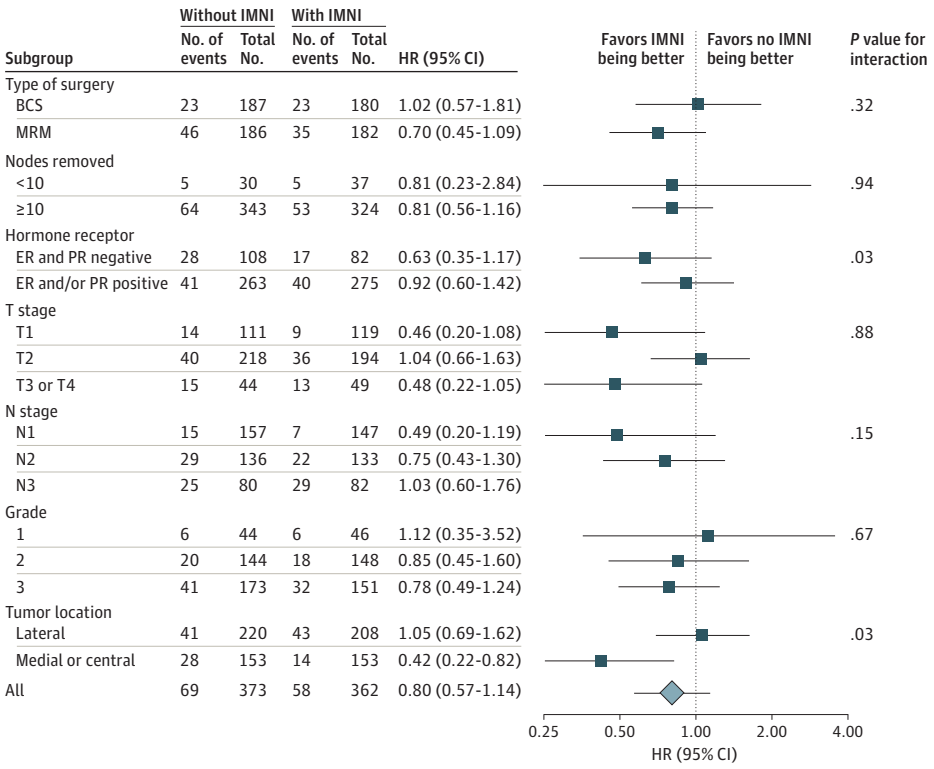
HR indicates hazard ratio; IMNI, internal mammary node irradiation.

detection of breast cancer by mass screening.[24] The previous Korean retrospective study included patients who were treated between 1994 and 2002, and most of these patients (86.6%) received either CMF (cyclophosphamide, methotrexate, and fluorouracil) or anthracycline-based chemotherapy.[21] A recent retrospective study of patients who were treated with taxane-based chemotherapy from the same institutions[25] also showed the benefit of IMNI, although the absolute survival was better than that reported in the previous study.[21] In addition, the percentage of patients with N1 disease was 12% in the previous study,[21] whereas in the current trial, the percentage was 41.4%. Accordingly, although a 7-year DFS rate of 70% was expected in the IMNI group, 85.3% was obtained in the current study.

Hence, the baseline risk of disease recurrence and the power to detect a between-group improvement in DFS were probably further reduced with the modern treatment. Furthermore, the incidental radiation doses to the IMNs and insufficient doses in the group treated without IMNI might have affected the outcome. A previous dummy run showed that the IMN area received 59% of the prescribed dose even if IMNI was not intended.[26] In the individual case review of this trial, the major deviation rates of radiotherapy plans were 23% in the group treated without IMNI and 22% in the group treated with IMNI.[27]

Among the subgroup of patients with mediocentrally located tumors (42% of the study population), DFS was improved by 10% in the IMNI group. The breast cancer mortality and DMFS were also significantly improved with IMNI in this subgroup. Therefore, we believe that the benefit of IMNI was affected by the tumor location and that patients with mediocentrally located tumors can be considered to receive IMNI when performing regional nodal irradiation. However, the subgroup analysis was not preplanned; thus, these findings should be interpreted with caution. The IMNs have lymphatic drainage that comes more often from inner than from outer quadrants.[28] The efferent lymphatic flow from the IMNs drains to the thoracic duct, the inferior deep cervical nodes, and the contralateral IMNs, which may lead to tumor cell dissemination.[29] The chance for distant metastasis can be further reduced by eradicating

Figure 3. Hazard Ratio (HR) for Disease Recurrence According to Subgroups



BCS indicates breast-conserving surgery; ER, estrogen receptor; HR, hazard ratio; IMNI, internal mammary node irradiation; MRM, modified radical mastectomy; and PR, progesterone receptor.

Table 2. Adverse Events

	Treated without IMNI (n = 373)					Treated with IMNI (n = 362)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
No. of patients with events (%)										
Arm edema	52	29	1	1	83 (22.3)	48	35	4	0	87 (24.0)
Brachial plexopathy	2	0	0	0	2 (0.5)	3	0	0	0	3 (0.8)
Radiation pneumonitis	12	0	0	0	12 (3.2)	13	9	0	0	22 (6.1)
Rib fracture	1	0	0	0	1 (0.3)	3	1	0	0	4 (1.1)
Skin reaction	61	6	1	0	68 (18.2)	56	7	1	0	64 (17.7)
Soft-tissue fibrosis and necrosis	4	1	0	0	5 (1.3)	4	1	0	0	5 (1.4)
Cardiac problem	3	2	0	0	5 (1.3)	5	2	1	0	8 (2.2)

Abbreviation: IMNI, internal mammary node irradiation.

cancer cells that drain toward the IMNs, particularly when a tumor is located in the inner quadrants.

In this trial, we found no differences in cardiac toxic effects between the 2 groups. However, the rates of cardiac toxic effects may increase with longer follow-up.

In addition, we evaluated only the role of IMNI in regional nodal irradiation, an approach that is similar to that used in the French trial.[10] Among the reported randomized clinical studies about regional nodal irradiation in breast cancer,[6,7,10] the current trial is the only study, to our knowledge, in which systemic treatments included taxanes and trastuzumab as the standard regimen, and 3-dimensional conformal radiotherapy based on CT simulation was performed in all patients. Thus, we were able to perform dosimetric analysis of the IMN area to estimate the association between the IMN dose and treatment outcome or the risk of toxic effects. Radiotherapy quality assurance through a dummy run and an individual case review was conducted in other studies and showed the variation in the IMN target delineation and radiotherapy planning among participating hospitals, which emphasized the need for education and monitoring.[26,27]

Limitations

This study has some limitations. First, the number of patients was insufficient to detect smaller differences in DFS attributed to more efficient systemic therapy and increasing proportion of early-stage breast cancers. Second, the follow-up period was relatively short, and additional longer-term follow-up is needed to confirm the findings. Third, the lack of central review of the radiotherapy plans before treatment for

each patient resulted in protocol violations in some cases, which hampered the aim of the study.

Conclusions

This trial raised the possibility of an improvement in DFS with regional nodal irradiation in patients with node-positive breast cancer who received IMNI compared with those who did not undergo IMNI. However, this improvement did not reach statistical significance, possibly because of a lower-than-anticipated event rate with a corresponding loss of statistical power. Nevertheless, the small benefits from IMNI cannot be ruled out, considering that the trial was designed to demonstrate a 10% benefit in the 7-year DFS. Furthermore, the findings suggest that including IMNI in regional nodal irradiation would be beneficial for patients with mediocentrally located tumors.

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