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ORIGINAL REPORT

DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

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ABSTRACT

Purpose

It is unknown whether irradiation of the internal mammary lymph nodes improves survival in patients with early-stage breast cancer. A possible survival benefit might be offset by radiation-induced heart disease. We assessed the effect of internal mammary node irradiation (IMNI) in patients with early-stage node-positive breast cancer.

Patients and Methods

In this nationwide, prospective population-based cohort study, we included patients who underwent operation for unilateral early-stage node-positive breast cancer. Patients with right-sided disease were allocated to IMNI, whereas patients with left-sided disease were allocated to no IMNI because of the risk of radiation-induced heart disease. The primary end point was overall survival. Secondary end points were breast cancer mortality and distant recurrence. Analyses were by intention to treat.

Results

A total of 3,089 patients were included. Of these, 1,492 patients were allocated to IMNI, whereas 1,597 patients were allocated to no IMNI. With a median of 8.9 years of follow-up time, the 8-year overall survival rates were 75.9% with IMNI versus 72.2% without IMNI. The adjusted hazard ratio (HR) for death was 0.82 (95% CI, 0.72 to 0.94; $P = .005$). Breast cancer mortality was 20.9% with IMNI versus 23.4% without IMNI (adjusted HR, 0.85; 95% CI, 0.73 to 0.98; $P = .03$). The risk of distant recurrence at 8 years was 27.4% with IMNI versus 29.7% without IMNI (adjusted HR, 0.89; 95% CI, 0.78 to 1.01; $P = .07$). The effect of IMNI was more pronounced in patients at high risk of internal mammary node metastasis. Equal numbers in each group died of ischemic heart disease.

Conclusion

In this naturally allocated, population-based cohort study, IMNI increased overall survival in patients with early-stage node-positive breast cancer.

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INTRODUCTION

Irradiation of the internal mammary lymph nodes (IMNI) has been a subject of controversy since radiotherapy to the chest wall/breast and regional lymph nodes was shown to improve survival in patients with early-stage breast cancer.[1-5] These nodes may harbor metastatic disease, especially in patients with a medially placed tumor or positive axillary nodes.[6] However, neither internal mammary node dissection nor radiotherapy has been proven beneficial.[7,8] Depending on treatment technique, IMNI increases the radiation dose to the heart, particularly on the left side.[9]

A recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis demonstrated the long-term effect of regional radiotherapy after mastectomy in patients with node-positive breast cancer. The absolute reduction in breast cancer mortality at 20 years was 7.9% in patients with one to three positive nodes, and the relative risk of dying from breast cancer was 0.80 (95% CI, 0.67 to 0.95; $P = .01$). Results were similar for patients with four or more nodes involved.[5] Two concurrent randomized trials on regional radiotherapy in early-stage breast cancer have shown results in favor of more regional radiotherapy.[10,11] In the European Organization for the Research and Treatment of Cancer (EORTC)

study 22922/10925, 4,004 patients were randomly assigned to arms with or without medial supraclavicular and IMNI.[12] In the MA.20 study, 1,832 patients were randomly assigned to whole-breast irradiation plus regional radiotherapy including IMNI versus whole-breast irradiation only after breast-conserving surgery.[11] Neither study could discern whether IMNI alone improved survival in early-stage node-positive breast cancer. The study populations consisted mainly of patients with no or one to three positive axillary nodes, so results may not apply to patients with more than three nodes involved.[11,12]

In the Danish Breast Cancer Cooperative Group (DBCG) 82b and 82c trials, IMNI was applied, and no excess risk of cardiac disease was noted.[13-15] Consequently, IMNI was the standard treatment for all Danish patients with node-positive breast cancer until 2003. At that time, it was suspected that IMNI and anthracyclines, used increasingly in the systemic adjuvant treatment of breast cancer, might interact unfavorably on the heart and counterbalance any beneficial effect of IMNI.[13] Therefore, IMNI was abandoned in patients with left-sided breast cancer but was continued in patients with right-sided breast cancer.[13] This could cause diminished survival in patients with left-sided breast cancer if there was a beneficial effect of IMNI large enough to outweigh the positive effect of decreasing heart doses in left-sided treatments. The DBCG-IMN study, which relied on this naturally random allocation of patients to IMNI or not, aimed to investigate whether IMNI increased overall survival in patients with early node-positive breast cancer.

PATIENTS AND METHODS

The study was designed as a nationwide, prospective, population-based cohort study. All six Danish departments and one German radiotherapy department that provided adjuvant radiotherapy to Danish patients with breast cancer participated. In Denmark, treatment of early-stage breast cancer follows national guidelines.[15a] Details on breast cancer diagnosis, treatment, and outcome in the population are reported prospectively to the DBCG registry.[16] The study was approved by the Danish Data Protection Agency. The scientific ethical committee of the central Denmark region waived the need for approval because of the nature of the study.

Patients

The study included Danish patients treated with radiotherapy after surgery for unilateral node-positive breast cancer from January 1, 2003, through December 31, 2007. To ensure a homogenously treated patient population, inclusion stopped with the introduction of taxanes as standard adjuvant systemic treatment. Patients who experienced recurrence before radiotherapy, were unfit for standard radiotherapy, had only micrometastatic nodes, were older than 70 years of age at operation, or had prior malignancy were excluded. Participation in other ongoing trials of the systemic treatment of breast cancer was allowed. Age and menopausal status at diagnosis were registered for each patient. Written informed consent was required for database entry.

Surgery was mastectomy or breast-conserving surgery, which both included axillary lymph node dissection of axillary level I and part of level II. The following were reported prospectively: tumor laterality and location within the breast; tumor size; histologic type; histologic grade (ductal and lobular carcinomas); estrogen receptor status and, if estrogen receptor negative, progesterone receptor status; number of metastatic nodes; and total number of nodes removed.

Standard systemic treatment in premenopausal patients with a hormone receptor–positive tumor was chemotherapy (cyclophosphamide, fluorouracil, and epirubicin or methotrexate) and 5 years of tamoxifen. Postmenopausal patients with a positive hormone receptor status received endocrine treatment (tamoxifen and, from June 2004, tamoxifen for 2.5 years followed by an aromatase inhibitor for 2.5 years). Patients with hormone receptor–negative disease received chemotherapy regardless of menopausal status.[16]

For all patients, regardless of cancer laterality, the radiotherapeutic dose to breast/chest wall, scar, supraclavicular nodes, infraclavicular nodes, and axillary levels II to III was 48 Gy in 24 fractions, administered in five fractions per week. If six or more axillary nodes contained macrometastases, axillary level I was treated. In patients with right-sided breast cancer, the internal mammary nodes in intercostal spaces one through four were treated with an anterior electron field or by inclusion in tangential photon fields (Data Supplement). A detailed description of the techniques used and the resulting doses to internal mammary nodes and organs at risk has been given elsewhere.[9,17]

Patients were observed with clinical examination biannually for 5 years and then annually for up to 10 years. If symptoms suspect of recurrence developed, additional tests were performed. Follow-up was completed and validated through linkage to patient records, the Danish Register on Causes of Death, and the Danish Central Populations Registry.

Statistical Analysis

The primary end point was overall survival. Survival time was defined as the time from commencement of radiotherapy to the date of death. Secondary end points were breast cancer mortality and distant recurrence. Time to death as a result of breast cancer was calculated from commencement of radiotherapy to death as a result of breast cancer, and the time to distant recurrence was calculated from commencement of radiotherapy to the diagnosis of distant recurrence. Times at risk were calculated from commencement of radiotherapy for comparability to other studies.[10]

The Kaplan-Meier product limit method was used to estimate survival rates. Estimates of cumulative incidence of breast cancer mortality and distant recurrence were made by taking competing events (ie, death as a result of causes other than breast cancer) into account. Patients were censored from follow-up for survival at January 1, 2014, and from follow-up for distant recurrence at the latest known recurrence-free date before or at January 1, 2014. Primary analyses of overall survival, breast cancer mortality, and distant recurrence were performed according to the intention-to-treat principle; hence, in the analyses descriptions, patients with right- and left-sided breast cancer are referred to as having received IMNI or not, respectively. Analyses that included only patients treated according to treatment allocation and with the start of time at risk at the date of surgery were undertaken. A Cox proportional hazards model was applied to provide adjusted and unadjusted estimates of hazard ratios (HRs) for all end points in patients with versus without IMNI. The following covariates were chosen and categorized on the basis of the literature: age at surgery (< 35, 35 to 49, 50 to 59, or ≥ 60 years), tumor size (≤ 20, 21 to 50, or ≥ 51 mm), number of positive nodes (1 to 3, 4 to 9, or ≥ 10), tumor grade (1, 2, or 3), tumor location (medial/central or lateral), and menopausal status (premenopausal or postmenopausal).[18] The number needed to treat was calculated as 1 divided by the absolute decrease in overall mortality at 8 years. Associations between treatment according to allocation and patient and tumor characteristics were analyzed with the Pearson's χ^2 test. All tests were two sided. P values less than .05 were considered significant. Statistical analyses were performed with STATA version 11.2 (StataCorp, College Station, TX).

RESULTS

Patient Population

From January 1, 2003, to December 31, 2007, 3,377 patients treated for early-stage node-positive breast cancer were included

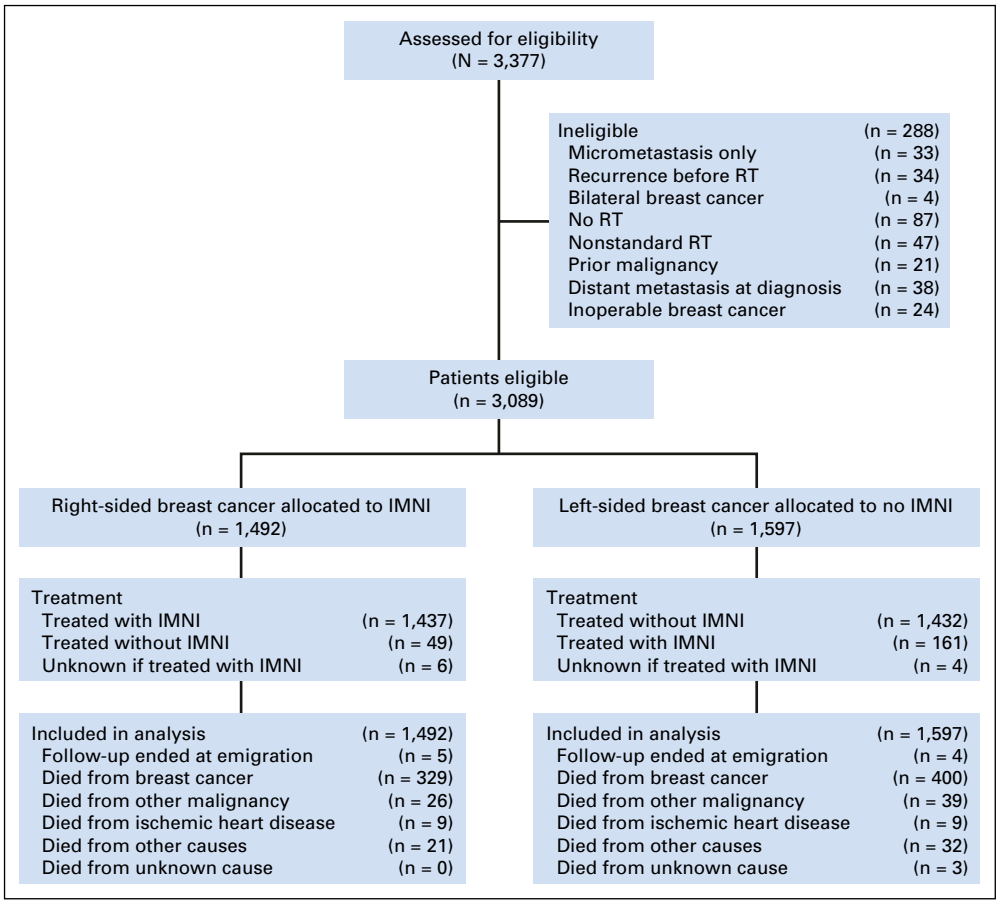

Fig 1. CONSORT diagram. IMNI, internal mammary node irradiation; RT, radiotherapy.

on the DBCG registry, 288 of whom were ineligible (Fig 1). Of the 3,089 patients remaining, 1,492 had right-sided and 1,597 had left-sided breast cancer. Baseline characteristics are listed in Table 1. In patients with right-sided breast cancer, 3% did not receive IMNI. Ten percent of patients with left-sided breast cancer did receive IMNI. These 10% more frequently had many lymph nodes involved or a medial/central tumor (Data Supplement). Time from surgery to radiotherapy was comparable with and without IMNI (Data Supplement).

Outcomes

The median follow-up time for overall survival was 8.9 years. At the time of analysis, 385 patients with and 483 patients without IMNI had died. The 8-year survival rates were 75.9% (95% CI, 73.6% to 78.0%) and 72.2% (95% CI, 69.9% to 74.4%) for patients with or without IMNI, respectively (Fig 2A). The adjusted HR for death with versus without IMNI was 0.82 (95% CI, 0.72 to 0.94; $P = .005$).

The median follow-up time for breast cancer mortality was 8.9 years. Death as a result of breast cancer occurred in 329 patients with and 400 patients without IMNI at the time of analysis. The cumulative incidences of breast cancer mortality at 8 years were 20.9% (95% CI, 18.8% to 23.0%) and 23.4% (95% CI, 21.3% to 25.5%) with versus without IMNI, respectively (Fig 2B), which resulted in an adjusted HR with versus without IMNI of 0.85 (95% CI, 0.73 to 0.98; $P = .03$).

The median follow-up time for distant recurrence was 8.3 years. Distant recurrence developed in 417 patients with and 478 patients without IMNI. The 8-year probabilities of experiencing a distant recurrence were 27.4% (95% CI, 25.1% to 29.8%) and 29.7% (95% CI, 27.4% to 32.0%) with or without IMNI, respectively (Fig 2C). The adjusted HR for distant recurrence with versus without IMNI was 0.89 (95% CI, 0.78 to 1.01; $P = .07$). Multivariable analysis showed that outcomes worsened for all end points with increasing tumor size, increasing number of positive axillary nodes, higher grade of malignancy, and medial/central tumor location. Age younger than 35 years and premenopausal status were associated with a higher hazard of distant recurrence (Data Supplement). Explorative analysis of the effect of IMNI within subgroups revealed no heterogeneity (Fig 3; Data Supplement). Similar numbers of patients died of ischemic heart disease in the two groups. The overall pattern of recurrence and causes of death are displayed in the Data Supplement. Analyses restricted to patients treated according to allocation to IMNI or not provided similar results (Data Supplement), as did analyses when the time at risk was counted from date of surgery (Data Supplement).

In an explorative analysis of subgroups defined by tumor location (lateral *v* medial/central) and number of macrometastatic

Table 1. Demographic and Clinical Characteristics

Characteristic	Breast Cancer Laterality: Right Side (n = 1,492) No.	%	Left Side (n = 1,597) No.	%
IMNI				
Yes	1,437	97	161	10
No	49	3	1,432	90
Unknown	6	< 1	4	< 1
Other radiotherapy				
Axillary level I treated	273	18	296	18
Boost to lumpectomy cavity	192	13	192	12
Type of surgery				
Mastectomy and axillary clearance	962	65	1,054	66
Breast conservation and axillary clearance	530	35	543	34
Type of systemic therapy				
Endocrine therapy	702	47	745	47
Chemotherapy	276	18	310	19
Both	514	35	542	34
Age at surgery, years				
< 35	37	2	40	2
35-49	421	28	433	27
50–59	534	36	578	36
≥ 60	500	34	546	34
Median (range)	56 (22-70)		56 (27-70)	
Menopausal status				
Premenopausal	612	41	649	41
Postmenopausal	880	59	948	59
Tumor size, mm				
0-20	625	42	653	41
21-50	773	52	836	52
> 50	92	6	106	7
Unknown	2	< 1	1	< 1
Tumor location*				
Medial or central	582	39	644	40
Lateral	907	61	950	59
Unknown	3	< 1	3	< 1
No. of positive lymph nodes				
1-3	868	58	950	60
4-9	401	27	417	26
≥ 10	223	15	230	14
No. of lymph nodes removed				
< 10	47	3	85	5
≥ 10	1,445	97	1,512	95
Median (interquartile range)	17 (14-22)		16 (13-20)	
Histologic type				
Invasive ductal carcinoma	1,311	88	1,356	85
Invasive lobular carcinoma	135	9	164	10
Other invasive type	46	3	77	5
Grade of malignancy†				
Grade 1	353	24	384	24
Grade 2	715	48	747	47
Grade 3	416	28	462	29
Unknown	8	< 1	3	< 1
Hormone receptor status				
Positive	1,207	81	1,279	80
Negative	285	19	318	20

Abbreviation: IMNI, internal mammary node irradiation.
*Medial or central defined as any tumor that involved breast tissue medial to a saggital plane through the nipple and/or tissue behind the areola.
†Grading was performed for ductal or lobular carcinoma; other histologic types were designated as grade 1.

axillary nodes (one to three nodes *v* four or more nodes), adjusted HRs for mortality were in favor of IMNI in the three subgroups of patients who had a medial/central tumor and/or four or more positive nodes (Fig 4; Data Supplement). When these three subgroups were combined, the 8-year survival rate was 72.2% (95% CI, 69.2% to 74.9%) with IMNI and was 64.8% (95% CI, 61.8% to 67.7%) without IMNI. The adjusted HR for death with versus without IMNI was 0.76 (95% CI, 0.66 to 0.89; $P = .001$). The number of patients needed to treat to avoid one death at 8 years was 14 (95% CI, 9 to 30).

DISCUSSION

In this population-based cohort study that included patients with early-stage node-positive breast cancer, IMNI was associated with an increase in overall survival of 3.7% at 8 years after treatment. Equal numbers of cardiac deaths occurred in the two groups. Breast cancer mortality decreased by 2.5% at 8 years, which showed that a decrease in the number of breast cancer deaths made up the larger part of the difference between the groups. Adjusted HRs with versus without IMNI were comparable for all end points (Data Supplement). Subgroup analyses suggested that the effect of IMNI was more pronounced in patients who had many nodes involved or who had a medial/central tumor (Fig 4). This analysis was prompted by results from studies on internal mammary node dissection: In a large surgical series, Huang et al[6] found that the risk of having internal mammary node metastases increased with the number of axillary nodes involved; 19% of patients with one to three nodes and 37% of patients with four or more positive axillary nodes had internal mammary nodes involved. Furthermore, the risk of internal mammary node metastases increased with medial/central tumor location.[6]

An EBCTCG meta-analysis on patients randomly assigned to regional radiotherapy or not after mastectomy from 1964 to 1986 showed equal-proportional reductions in the risk of recurrence and breast cancer mortality in patients who had one to three and four or more axillary nodes involved.[5] Other recent trials have reported results in favor of regional radiotherapy: In the EORTC 22922/10925 study, 4,004 patients were randomly assigned from 1996 to 2004 to IMNI or not in intercostal spaces 1 to 3 (or spaces 1 to 5 in patients with lower medial tumors) and medial supraclavicular nodes.[12] At 10 years, improvements of 1.6% in overall survival (HR, 0.87; 95% CI, 0.76 to 1.00; $P = .05$) and 1.9% in breast cancer mortality (HR, 0.82; 95% CI, 0.70 to 0.97; $P = .02$) were observed with radiotherapy.[10] The study population overall had a low risk of internal mammary node metastasis; 44% of patients had axillary node–negative disease and a medial tumor location, and 43% had one to three positive nodes.[6,12] This, and the low overall recurrence rate in the study, may explain the smaller gain in survival compared with the 3.7% found in our study. In the MA.20 study, 1,832 patients were randomly assigned from 2000 to 2007 to breast or breast plus regional radiotherapy, including IMNI after breast-conserving surgery and axillary dissection. At 10 years, the rates of both locoregional and distant disease-free survival improved with regional radiotherapy, by 3.0% (HR, 0.59; 95% CI, 0.39 to 0.88; $P = .009$) and 3.9% (HR, 0.76; 95% CI, 0.60 to 0.97; $P = .03$), respectively. However, improvements in overall survival (1.0%; HR, 0.91; 95% CI, 0.72 to 1.13; $P = .38$) and breast cancer mortality (2.0%; HR, 0.80; 95% CI, 0.61 to 1.05; $P = .11$) were not statistically significant.[11] From 1991 to 1997, Hennequin et al[8] randomly assigned 1,334 patients with positive axillary nodes

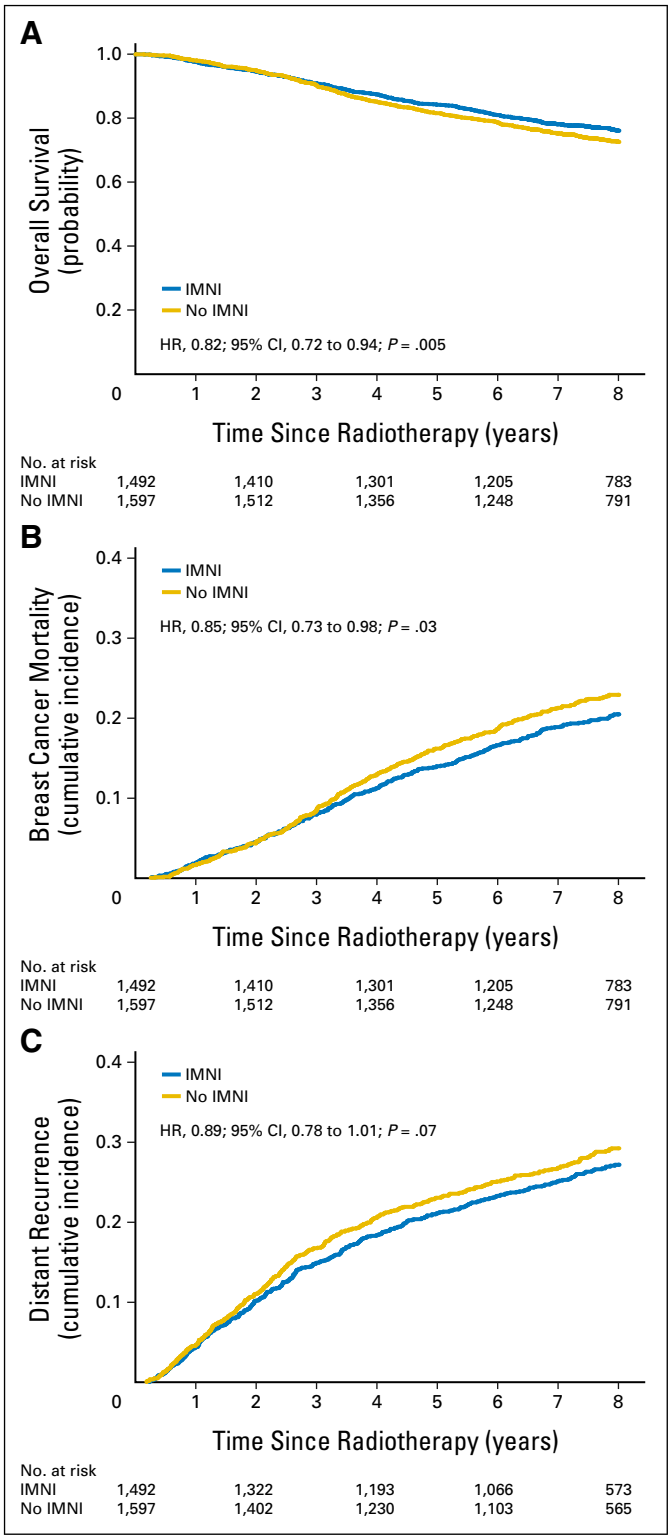

Fig 2. Kaplan-Meier estimates and associated hazard ratios (HRs) of (A) overall survival, (B) cumulated incidence of breast cancer mortality, and (C) distant recurrence in patients with and without internal mammary node irradiation (IMNI).

(75%) and/or medial/central tumors to IMNI or not after mastectomy and observed a statistically nonsignificant improvement of 3.3% in overall survival at 10 years.[8]

Results from observational studies on IMNI have been conflicting: in some, patients with medial/central tumors benefitted from treatment, whereas, in others, no effect was detected.[7,19-21] Common to all these studies is a nonrandomized design, which often results in confounding from unbalanced prognostics in treatment groups. A strength of the current study was that the decision to provide IMNI was based on cancer laterality. Because cancer laterality does not affect survival in patients with breast cancer who are not treated with radiotherapy, this would be expected to distribute potential confounders equally between treatment groups, which would result in a level of internal validity not usually achievable in a population-based study.[22] The rate of major coronary events, including ischemic heart death, has been found to be dependent on the mean heart dose.[23] The negative effect of cardiac irradiation may be aggravated by the addition of chemotherapy, which was used in greater than half of our patients.[24,25] In the current study, the use of tangential techniques after breast-conserving surgery resulted in higher mean heart doses on the left side. In patients treated with mastectomy, the use of a separate electron field for IMNI resulted in heart doses that were higher in right-sided treatments.[9,17] However, HRs for overall survival with or without IMNI were independent of the type of surgery, so it is unlikely that radiation-induced cardiotoxicity contributed to the difference observed in overall survival (Data Supplement).

The national population-based design of the study should ensure unbiased inclusion of patients and high external validity of results. This design also resulted in the inclusion of a large number of patients with four or more nodes involved, which was not achieved in randomized clinical trials.[10] However, the exclusion of patients unfit to receive standard radiotherapy may have led to an overestimation of the treatment effect. Another limitation to the study was the lack of evaluation of radiation-induced morbidity, both cardiac and other, that had not yet resulted in death. Because IMNI was avoided in patients with left-sided breast cancer, we can make no conclusions on the potential cost of IMNI in terms of cardiotoxicity in these patients. Also, *HER2* status and indicators of patient health (eg performance status) were not systematically reported, so no adjustment for these factors could be made in the multivariable analysis, nor could we relate outcomes to molecular subtypes.[26]

In summary, in this large, population-based cohort study on patients with node-positive breast cancer who were treated with commonly used techniques in daily clinical practice, IMNI improved survival. The effect of treatment seemed to depend on the risk of internal mammary node metastases. Other recent trials on regional irradiation in early-stage breast cancer have consistently provided results in favor of more regional irradiation.[10,11] However, these results, as well as those from the current study, might not readily apply to the breast cancer patient population of today. Advances in surgery and the systemic treatment of early-stage breast cancer have reduced recurrence rates, and breast cancer screening may mean that more cancers with less aggressive biology are detected.[27,28] This is likely to reduce the absolute gains achievable with regional radiotherapy. Furthermore, not only the risk of radiation-induced cardiovascular disease but also the risk of inducing second cancers should be considered.[29] Conversely, techniques

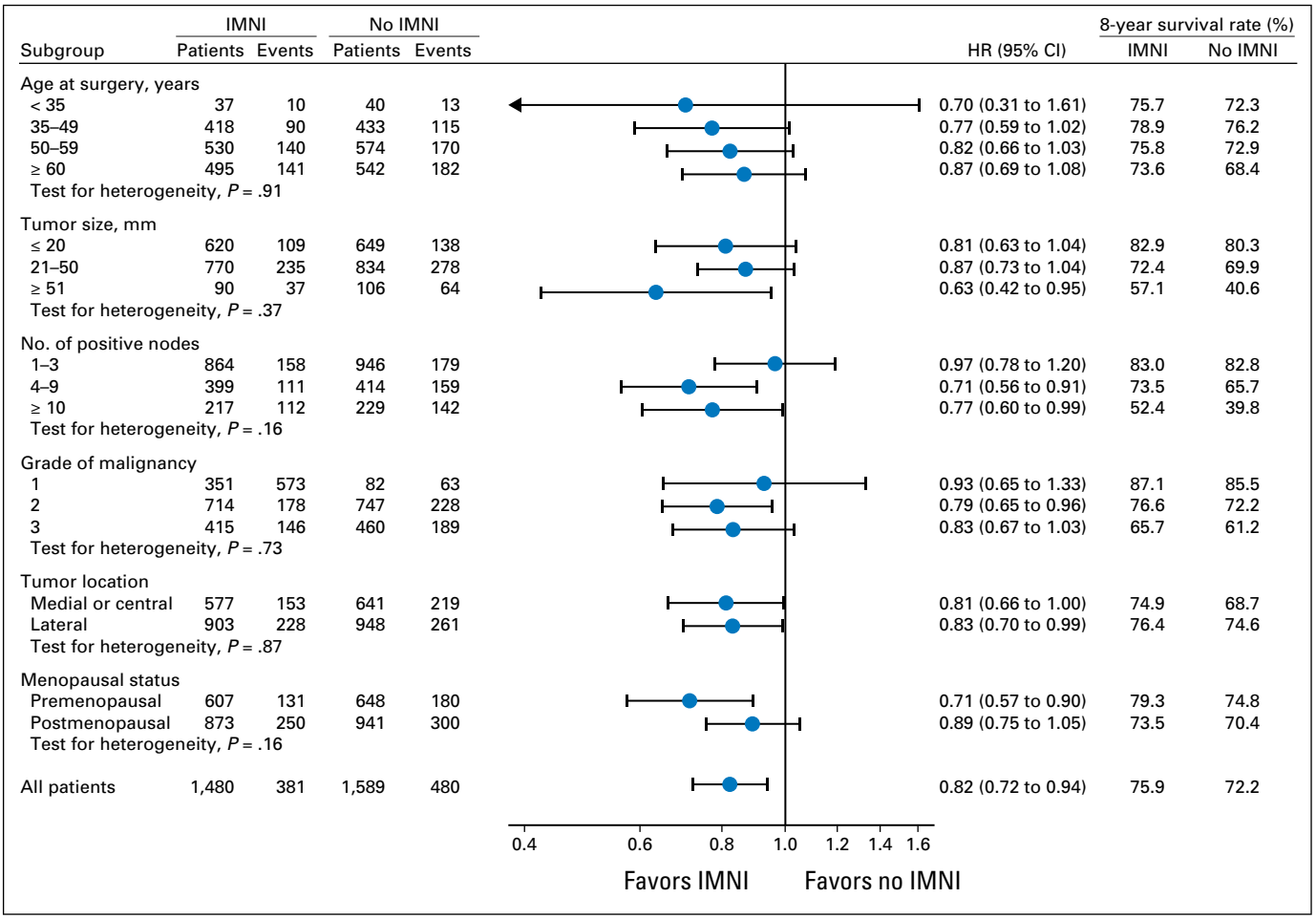

Fig 3. Overall survival rates and corresponding hazard ratios (HR) with versus without internal mammary node irradiation (IMNI) within subgroups in the multivariate Cox proportional hazards model. Information on covariates was complete in 3,069 patients.

for organ-sparing delivery of radiotherapy have developed rapidly during recent years, which reduces the risk of toxicity.[30] The increasing efficiency of systemic treatment and radiotherapy might increase the relative gains with radiotherapy.[5] Results from clinical trials will forever be lagging behind developments in clinical practice, so it is unlikely that new trials of IMNI will be

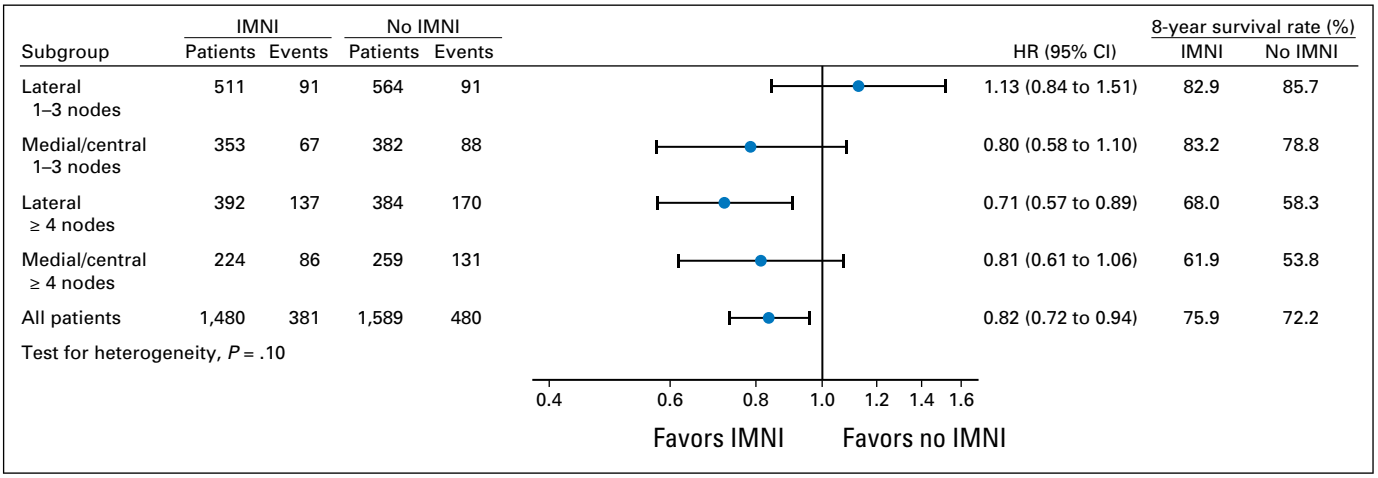

Fig 4. Overall survival rates and corresponding hazard ratios (HR) with versus without internal mammary node irradiation (IMNI) within subgroups defined by tumor location and the number of axillary nodes involved.

more useful for decision making about which patients should be offered the treatment. Instead, it might be more sensible to select patients for IMNI on the basis of the balance among the individual patient's risk of recurrence, internal mammary node metastases, and late toxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

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Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

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