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Article

Side Effects 15 Years After Lymph Node Irradiation in Breast Cancer: Randomized EORTC Trial 22922/10925

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ARTICLE

Abstract

Background: Uncertainty about the benefit–risk ratio of regional lymph node irradiation led to varying clinical protocols. We investigated long-term late side effects after internal mammary and medial supraclavicular (IM-MS) lymph node irradiation to improve shared decision making. **Methods:** The multicenter European Organization for Research and Treatment of Cancer trial (ClinicalTrials.gov, NCT00002851) randomly assigned stage I-III breast cancer patients with involved axillary nodes and/or a medially located primary tumor. We analyzed late side effects both longitudinally at every follow-up and cross-sectionally at 5-year intervals. All statistical tests were 2-sided. **Results:** Between 1996 and 2004, 46 departments from 13 countries accrued 4004 patients. Median follow-up was 15.7 years. Longitudinal follow-up data showed cumulative incidence rates at 15 years of 2.9% (95% confidence interval [CI] = 2.2% to 3.8%) vs 5.7% (95% CI = 4.7% to 6.9%) ($P < .001$) for lung fibrosis, 1.1% (95% CI = 0.7% to 1.7%) vs 1.9% (95% CI = 1.3% to 2.6%) ($P = .07$) for cardiac fibrosis, and 9.4% (95% CI = 8.0% to 10.8%) vs 11.1% (95% CI = 9.6% to 12.7%) ($P = .04$) for any cardiac disease when treated without or with IM-MS lymph node irradiation. There was no evidence for differences between left- and right-sided breast cancer (Wald χ^2 test of treatment by breast side interaction, $P = .33$ and $P = .35$, for cardiac fibrosis and for any cardiac disease, respectively). The cumulative incidence probabilities of cross-sectionally reported side effects with a score of 2 or greater at 15 years were 0.1% (95% CI = 0.0% to 0.5%) vs 0.8% (95% CI = 0.4% to 1.4%) for pulmonary ($P = .02$), 1.8% (95% CI = 1.1% to 2.8%) vs 2.6% (95% CI = 1.8% to 3.7%) for cardiac ($P = .15$), and 0.0% (95% CI not evaluated) vs 0.1% (95% CI = 0.0% to 0.4%) for esophageal ($P = .16$), respectively. No difference was observed in the incidence of second malignancies, contralateral breast cancer, or cardiovascular deaths. **Conclusions:** The incidence of late pulmonary side effects was statistically significantly higher after IM-MS lymph node irradiation, as were some of the cardiac events, without a difference between left- and right-sided treatments. Absolute rates and differences were very low, without increased non-breast cancer–related mortality, even before introducing heart-sparing techniques.

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Box 1. Side effects recorded during follow-up on the annual CRF 4 and on the 5-yearly CRF 10[a]

Form 4, to be completed once a year or if an event occurred

Date of examination or of last contact: (day/month/year)

ECOG/WHO performance: (0-4)

Late toxicity

- Any clinical evidence of lung fibrosis? (0 = no, 1 = yes)
- Any clinical evidence of cardiac fibrosis? (0 = no, 1 = yes)
- Other late toxicity? (0 = no, 1 = yes)
- If yes, please specify

Cardiac diseases

- Any evidence of cardiac diseases? (0 = no, 1 = yes)
- If yes, please specify

Form 10, to be completed every 5 years after treatment

Date of assessment: (day/month/year)

Heart Late RT Morbidity Scoring: (0-4)

- 0 = no change from baseline
- 1 = asymptomatic or mild symptoms; transient T-wave inversion and ST changes; sinus tachycardia >110 (at rest)
- 2 = moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T-wave and ST changes; low QRS
- 3 = severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; ECG abnormalities
- 4 = tamponade severe heart failure/severe constrictive pericarditis

Lung Late RT Morbidity Scoring: (0-4)

- 0 = no change from baseline
- 1 = asymptomatic or mild symptomatic or mild symptoms (dry cough); slight radiographic appearances
- 2 = moderate symptomatic fibrosis or pneumonitis (severe cough); low-grade fever; patchy radiographic appearances
- 3 = severe symptomatic fibrosis of pneumonitis; dense radiographic changes
- 4 = severe respiratory insufficiency/continuous O_2/assisted ventilation

Esophagus Late RT Morbidity Scoring: (0-4)

- 0 = no change from baseline
- 1 = mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing
- 2 = unable to take solid food normally; swallowing semi-solid food; dilation may be indicated
- 3 = severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required
- 4 = necrosis/perforation; fistula

Other late radiation toxicity: (0 = no, 1 = yes)

- If yes, specify (please use CTC toxicity scale-version 2)

[a]See Supplementary Figure 1 (available online) for CRF 4 and Supplementary Figure 2, (available online) for the 5-yearly CRF 10.
CRF = case report form; CTC = Common Toxicity Criteria, ECG = electrocardiogram; ECOG/WHO = Eastern Cooperative Oncology Group/World Health Organization; RT = radiation therapy; T, ST, QRS = ECG readings.

Radiation therapy improves loco-regional tumor control for all breast cancer patients, and decreases breast cancer related mortality in node-positive and some high-risk node-negative patients (1,2). However, an overview of randomized trials conducted in the 1950s-1970s showed a non-statistically significant trend for decreased overall survival after 15 years of follow-up (3,4). It was concluded that the benefits of radiation therapy might be jeopardized by serious late side effects. Especially the use of internal mammary lymph node irradiation was considered to contribute to an increased rate of cardiovascular morbidity and mortality (5). Other studies demonstrated a substantial beneficial effect on overall survival for high-risk patients as hypothesized by avoiding secondary dissemination from subclinical tumor deposits in untreated lymph nodes (6,7). This controversy resulted in varying policies, with some centers continuing to treat internal mammary lymph nodes in high-risk patients, whereas others irradiated only the axilla and the medial supraclavicular lymph nodes to avoid radiation to the heart.

Further support in favor of comprehensive lymph node irradiation, including the internal mammary lymph nodes, in high-risk cases led to the initiation of several studies (8–11). Ten-year results showed, overall, an improved disease-free and distant disease-free survival, with reduced breast-cancer mortality and a varying effect on overall survival after regional nodal irradiation (12–15).

For the randomized, phase 3, multicenter European Organisation for Research and Treatment of Cancer (EORTC) trial 22922/10925 (Clinicaltrials.gov NCT00002851) that investigated the impact on overall survival of elective internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer, the second of 2 scheduled analyses at a median follow-up of 15.7 years showed a statistically significant reduction of breast cancer mortality and breast cancer recurrence by IM-MS irradiation, which was not converted into improved overall survival (12,16). In this article, we present a detailed analysis of the late side effects.

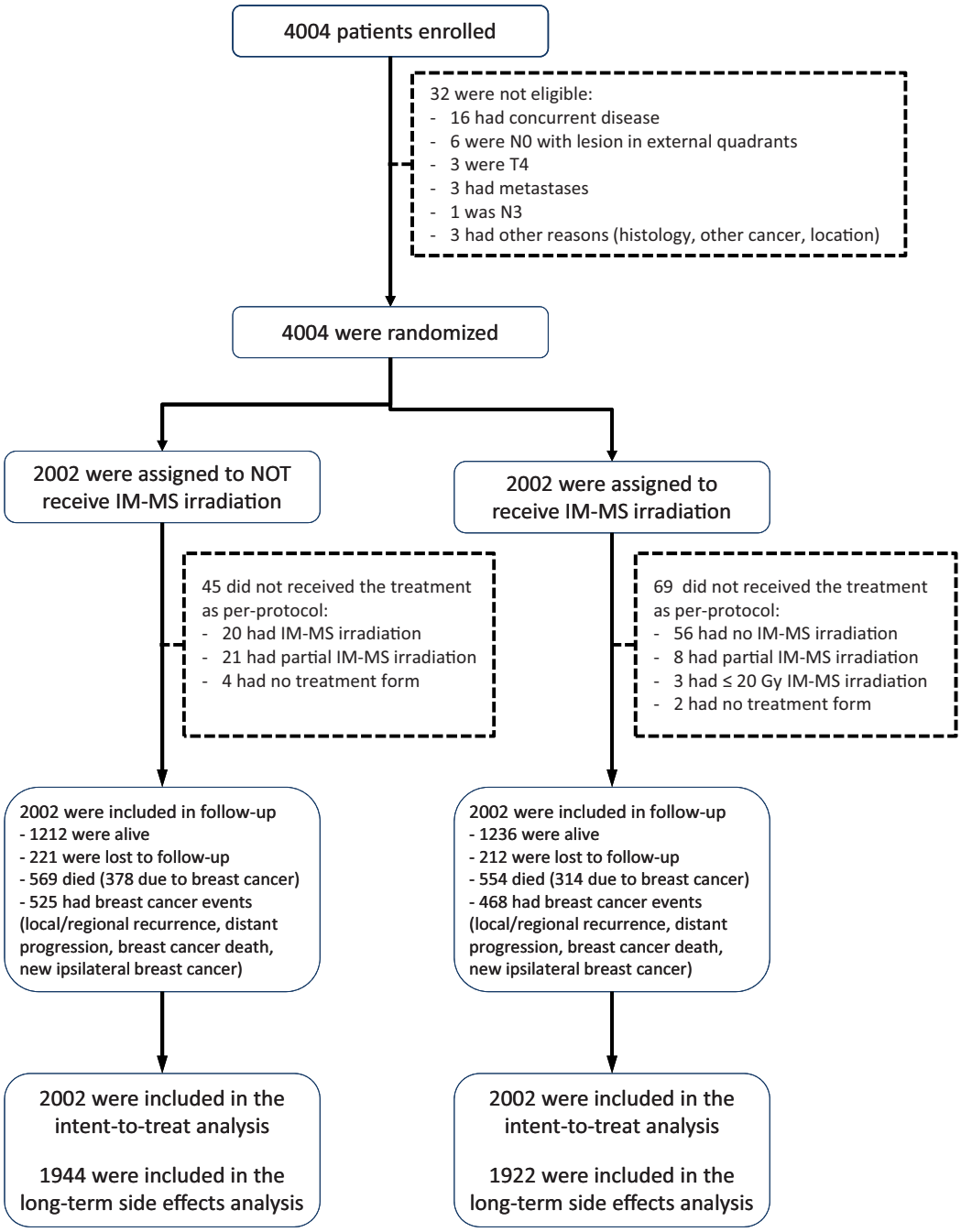

Figure 1. CONSORT flow diagram graphically displaying the enrolment and follow-up of the study patients. Follow-up status at the clinical cut-off date of the final analysis. Long-term side effect analysis includes eligible patients who received the allocated treatment.

Methods

Patients

The study design of the multicenter, randomized, phase 3 EORTC trial 22922/10925 was previously reported (12). Eligibility criteria included unilateral histologically confirmed adenocarcinoma stage I-III breast cancer with a primary tumor located centrally or medially in the breast, irrespective of axillary involvement, or a primary tumor located in the external quadrants combined with axillary lymph node involvement. Patients after both mastectomy and breast-conserving surgery could participate. After the introduction of the sentinel lymph node procedure during the last years of the trial, this procedure—followed by an axillary dissection in case of involved sentinel lymph nodes—was allowed next to primary axillary lymph node dissection. Patients were centrally randomly assigned to irradiation or not of the IM-MS lymph nodes. The prescribed total dose was 50 Gy in 25 fractions of 2 Gy over 5 weeks. A minimization algorithm with a 1:1 ratio was used for the randomization, taking into account the following stratification factors: center, menopausal status, site of the primary tumor within the breast, type of breast surgery, type of axillary dissection as stated by the surgeon, pathological T-stage, and

Table 1. Cumulative incidence rates at 15 years of late side effects for all patients in the per-protocol population according to the allocated treatment and laterality

Late side effect	Treatment		
	No IM-MS (n = 1944) Rate (95% CI), %	IM-MS (n = 1922) Rate (95% CI), %	*P*
Clinical evidence of lung fibrosis	2.9 (2.2 to 3.8)	5.7 (4.7 to 6.9)	<.001[a]
Clinical evidence of cardiac fibrosis	1.1 (0.7 to 1.7)	1.9 (1.3 to 2.6)	.07[a]
Right-sided breast cancer	0.6 (0.2 to 1.3)	1.9 (1.1 to 3.1)	.07[b]
Left-sided breast cancer	1.6 (0.9 to 2.6)	1.8 (1.1 to 2.9)	
Any evidence of cardiac diseases	9.4 (8.0 to 10.8)	11.1 (9.6 to 12.7)	.04[a]
Right-sided breast cancer	8.3 (6.5 to 10.3)	10.8 (8.8 to 13.1)	.04[b]
Left-sided breast cancer	10.5 (8.5 to 12.7)	11.3 (9.2 to 13.6)	

[a]Two-sided Gray test. CI = confidence interval; IM-MS = internal mammary–medial supraclavicular irradiation.
[b]Two-sided *P* value for treatment effect, obtained using a Fine and Gray model adjusted for left and right side. Test of treatment by left- and right-side interaction: 2-sided *P* value = .33 and .35 for cardiac fibrosis and cardiac diseases, respectively.

pathological N-stage. Sample sizes were calculated based on overall survival, the primary endpoint. Study approval was provided by the participating departments' ethical committees, and written informed consent was obtained from all patients.

After treatment completion, patients were seen annually for the first 5 years and thereafter every 2 years or until the date of recurrence or death. Concerning side effects, when designing the trial in 1992, we originally planned to score only the performance status, the presence of any clinical evidence of lung or cardiac fibrosis, and any evidence of cardiac disease using conventional longitudinal follow-up (Supplementary Figure 1, available online), without any routinely scheduled follow-up examinations. After initiation of trial accrual, we launched a supplementary prospective project for a more detailed evaluation of the incidence of late side effects, recording cardiac, pulmonary, and esophageal side effects according to the Common Terminology Criteria for Adverse Events version 2 cross-sectionally every 5 years during follow-up (Supplementary Figure 2, available online). Box 1 summarizes the recorded side effects. Reporting of data on the case report form (CRF) was continuously followed-up at the EORTC headquarters, with reminders being sent in case of delays as well as personal contacts by the study coordinators if required to optimize compliance by actively updating the follow-up of all patients, using a multitude of sources, including patients or their proxies, general practitioners, and other treating physicians. This "synchronizing" and "updating" of the follow-up, both at the occasion of the 10- and 15-year analyses, minimized a possible influence of missing data. All data were analyzed using cumulative incidence curves. Time to late side effects was defined as the time interval between the date of random assignment and the date of the first assessment of the side effect. Only the first event was taken into account; death was considered as a competing risk.

Results on the 15-year primary and secondary tumor-outcome–related endpoints, overall survival, disease-free survival, distant metastases-free survival and breast cancer mortality were published recently (16).

Statistical Analysis

The evaluation of the rates of side effects was done including only the eligible patients that were treated per-protocol included (n = 3866 of 4004 [96.6%]). Inferential tests were conducted to assess whether the differences were beyond random fluctuations. Cumulative incidence curves were compared using Gray's test. The homogeneity of differences across the left and right breast was tested using the Fine and Gray model, including a term for treatment by side interaction. All tests were 2-sided, and a *P* of less than .05 was considered statistically significant, with no adjustment for multiplicity. Estimates are provided with their 2-sided 95% confidence intervals.

Results

Between July 1996 and January 2004, 46 radiation oncology departments from 13 countries accrued 4004 patients. The CONSORT flow diagram is displayed as Figure 1. A detailed overview of patient-, tumor-, and treatment-related characteristics, which did not differ between groups, is given in Supplementary Table 1 (available online). Median age at study entry was 54 years; 34.1%, 52.3%, and 13.7% had stage I, II, and III breast cancer, respectively. The majority of patients (76.7%) were treated with breast-conserving therapy, including breast irradiation. Chest wall irradiation was given to 73.4% of the patients receiving mastectomy. Nearly all lymph node-positive (99.0%) and 66.3% of lymph node-negative patients received adjuvant systemic treatment. IM-MS irradiation was given in 1944 (97.1%) of the patients randomly assigned to receive it and in 41 (2.0%) patients randomly assigned not to receive it.

Table 1 and Figure 2 show the 15-year cumulative incidence rates of late side effects in the per-protocol population according to the allocated treatment and laterality, as scored annually using the conventional CRF (Supplementary Figure 1, available online). Cumulative incidence of lung fibrosis at 15 years was 2.9% (95% CI = 2.2% to 3.8%) vs 5.7% (95% CI = 4.7% to 6.9%) (Gray's test, $P < .001$), cardiac fibrosis 1.1% (95% CI = 0.7% to 1.7%) vs 1.9% (95% CI = 1.3% to 2.6%) (Gray's test, $P = .07$), and any cardiac disease 9.4% (95% CI = 8.0% to 10.8%) vs 11.1% (95% CI = 9.6% to 12.7%) (Gray's test, $P = .04$), respectively, for patients without vs with IM-MS irradiation. There was a higher incidence of deaths in the absence of lung fibrosis in patients without compared with IM-MS irradiation (Gray's test, $P = .04$, data not shown), potentially preventing the observation of lung fibrosis in this arm and possibly explaining the higher incidence in the IM-MS arm. There was no statistically significant difference in the incidence of competing risks, that is, deaths in absence of cardiac fibrosis or cardiac disease (data not shown). No differences for cardiac side effects between left- and right-sided breast cancer were noted (Wald χ^2 test of treatment by breast side interaction, $P = .33$ and $P = .35$, for cardiac fibrosis and for any cardiac disease, respectively).

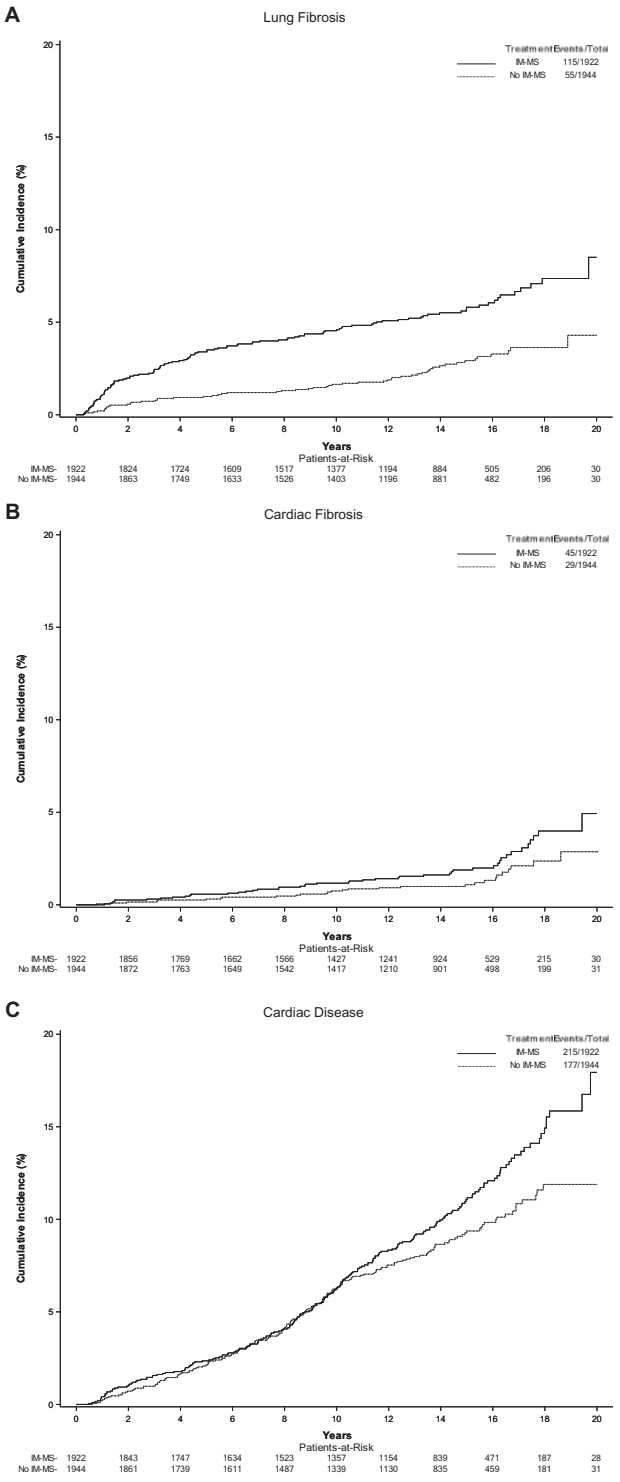

Figure 2. Cumulative incidence rates over time (all patients in the per protocol population) for lung fibrosis (A), cardiac fibrosis (B) and cardiac disease (C). IM-MS = internal mammary-medial supraclavicular irradiation.

Supplementary Figure 3 (available online) shows the cumulative number of cross-sectional late-effect forms. We received, according to the time since random assignment, 6489 forms in total: 2679 (77.5%) of the 3457 patients alive or with follow-up at 5 years, 66.8% (1934 of 2896) at 10 years, and 61.6% (911 of 1479) at 15 years, respectively. The cumulative incidences of cross-sectionally reported late cardiac, pulmonary, and esophageal

Table 2. Cumulative incidence rates at 15 years of late radiation therapy morbidities over time, per score (all patients in the per-protocol population)[a]

Late side effect	Rate (95% CI), %	
	No IM-MS (n = 1944)	IM-MS (n = 1922)
Cardiac late RT morbidity score		
≥ 1	3.9 (2.9 to 5.1)	4.5 (3.4 to 5.8)
≥ 2	1.8 (1.1 to 2.8)	2.6 (1.8 to 3.7)
≥ 3	1.1 (0.6 to 1.8)	1.0 (0.5 to 1.7)
≥ 4	0.3 (0.1 to 0.7)	0.1 (0.0 to 0.5)
Lung late RT morbidity score		
≥ 1	2.5 (1.7 to 3.6)	3.7 (2.8 to 4.9)
≥ 2	0.1 (0.0 to 0.5)	0.8 (0.4 to 1.4)
≥ 3	0.0 (NE-NE)	0.2 (0.0 to 0.7)
≥ 4	0.0 (NE-NE)	0.1 (0.0 to 0.7)
Esophageal late RT morbidity		
≥ 1	0.7 (0.4 to 1.3)	1.1 (0.7 to 1.8)
≥ 2	0	0.1 (0.0 to 0.4)
≥ 3	0	0.1 (0.0 to 0.4)
≥ 4	0	0

[a]CI = confidence interval; IM-MS = internal mammary–medial supraclavicular irradiation; NE = Not Evaluated; RT = Radiation Therapy.

side effects are displayed in Table 2. In summary, the cumulative rates of any side effect after 15 years of follow-up were 2.5% (95% CI = 1.7% to 3.6%) vs 3.7% (95% CI = 2.8% to 4.9%) for pulmonary ($P = .01$), 3.9% (95% CI = 2.9% to 5.1%) vs 4.5% (95% CI = 3.4% to 5.8%) for cardiac ($P = .26$), and 0.7% (95% CI = 0.4% to 1.3%) vs 1.1% (95% CI = 0.7% to 1.8%) for esophageal ($P = .59$) for patients without or with IM-MS irradiation, respectively. There was no statistically significant difference in the incidence of competing risks, that is, deaths in absence of pulmonary, cardiac, or esophageal side effects (data not shown). The cumulative incidence probabilities of clinically relevant scores of 2 or greater at 15 years were 0.1% (95% CI = 0.0% to 0.5%) vs 0.8% (95% CI = 0.4% to 1.4%) for pulmonary ($P = .02$), 1.8% (95% CI = 1.1% to 2.8%) vs 2.6% (95% CI = 1.8% to 3.7%) for cardiac ($P = .15$), and 0.0% (CI not evaluated) vs 0.1% (95% CI = 0.0% to 0.4%) for esophageal ($P = .16$), respectively (Figure 3).

No differences between treatment arms for the worst World Health Organization performance score during follow-up and before any progression of the disease or new disease (Supplementary Table 2, available online) were noted. Supplementary Table 3 (available online) shows 563 second primary cancers among the 3866 patients (14.6%), 255 of which were contralateral breast cancers (6.6%). No difference in the frequency of secondary cancers between the treatment arms was observed during follow-up. Supplementary Table 4 (available online) displays the survival and follow-up status, including the cause of death, if applicable, showing as the only difference a lower death rate due to breast cancer after IM-MS irradiation: 15.5% (95% CI = 13.8% to 17.1%) vs 18.7% (95% CI = 16.9% to 20.4%). The rate of unknown causes and missing data was higher in the nodal irradiation treatment arm: combined 2.1% (95% CI = 1.5% to 2.8%) vs 3.4% (95% CI = 2.6% to 4.2%).

Discussion

The per-protocol analysis on clinically relevant late side effects of at least grade 2 for the 3866 eligible patients without or with

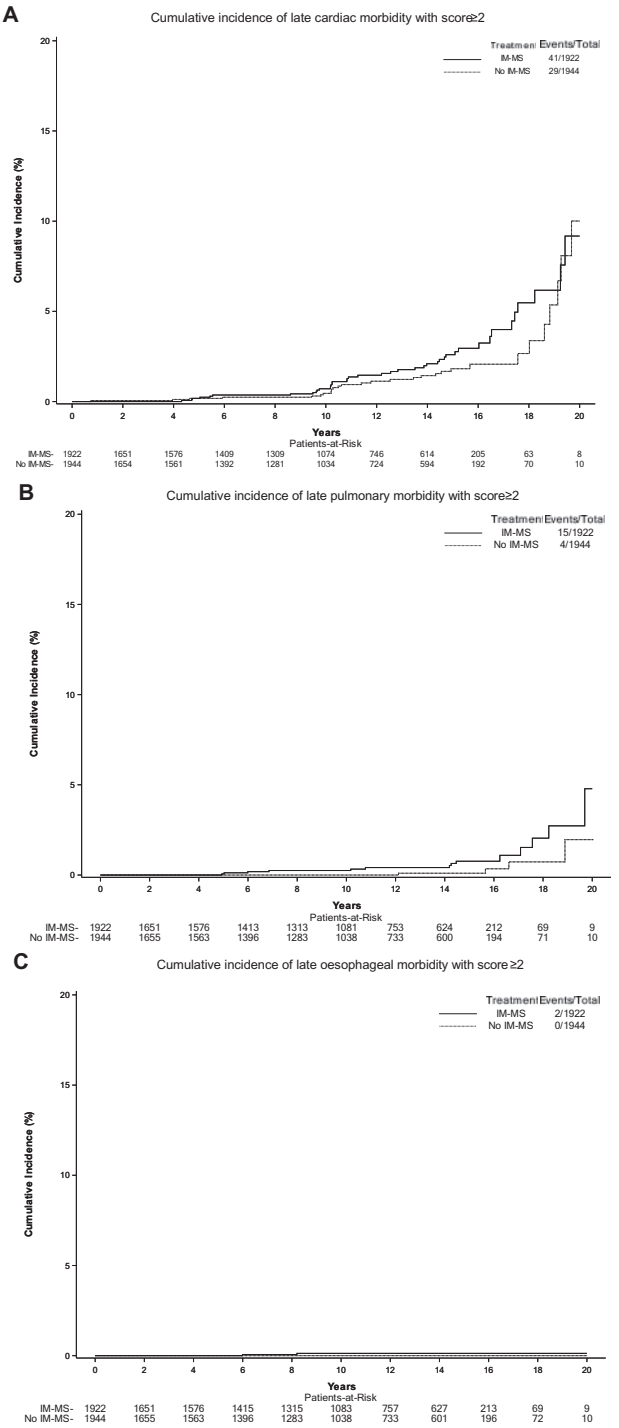

Figure 3. Cumulative incidence rates of late radiation therapy morbidities with score greater than or equal to 2 over time (all patients in the per-protocol population) for cardiac morbidity (A), pulmonary morbidity (B) and esophageal morbidity (C). IM-MS = internal mammary-medial supraclavicular irradiation.

IM-MS lymph node irradiation who received the allocated treatment showed a statistically significant difference between cross-sectionally scored cumulative incidence rates of clinically relevant scores of 2 or greater at 15 years for pulmonary morbidity (0.1% vs 0.8%), whereas the differences for cardiac (1.8% vs 2.6%) and esophageal morbidity(0.0% vs 0.1%) were statistically non-significant. When focusing on differences in severe grade 3-4 toxicity, extremely low rates without differences between the treatment arms were observed. For the conventional longitudinally scored side effects after 15 years of follow-up, statistically significant differences were only noted for cumulative rates of "pulmonary fibrosis," increasing by 2.8% (from 2.9% to 5.7%) and for "any cardiac disease," increasing by 1.7% (from 9.4% vs 11.1%), without left- or right-sided treatment differences. So, in summary, we found very low absolute values with small differences between the treatment arms for all late side effects. This is in agreement with the lack of differences in cardiac mortality, in the rate of second cancers, and in World Health Organization performance scores after treatment (16). Of note, the parallel-running, annual, conventional longitudinal scoring of side-effects with the more detailed cross-sectional 5-annually reporting—both analyzed cumulatively—did offer additive detailed information and the opportunity to compare rates of side effects based on different scoring systems and intervals, thus verifying acute side effects being potentially reversible during an extensive follow-up (Supplementary Figures 1 and 2, available online).

The observed rates of any cardiac disease, as displayed in Table 1, reflect a combination of a median patient age of 54 years at study entry, with a median age of 69.7 years after 15.7 years of follow-up and an overreporting from minor events such as hypertension. The observed low rates and differences between treatment arms of cardiac disease and cardiac deaths do not seem in line with the findings of Darby et al. (17) They demonstrated in a population-based case–control study a relative increase of major coronary events by 7.4% per Gy mean heart dose without a threshold dose. These findings were derived from patients treated in Sweden and Denmark between 1958 and 2001, with radiation doses to the heart estimated from treatment charts. Their conclusions were confirmed in several other studies using various irradiation techniques, follow-up times, and methods to estimate the cardiac doses, resulting in a range of relative risk increases between 6.4% and 19.0% per Gy (18–20). We emphasize that these studies found a proportional and not absolute increase; with a baseline risk of 10%, a 7% increase per Gy implies a total risk of 10.7% after a mean heart dose of 1 Gy.

All this led to a still-ongoing debate about the translation of these findings into daily clinical practice, which is challenged also by the introduction of contemporary modern radiation therapy approaches, including target volume–based treatment set-up and respiratory control (17,21,22). Importantly, this considerable risk, starting within 5 years after radiation therapy, was not present in the more recently published studies evaluating lymph node irradiation (12–14). Moreover, the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) concerning lymph node irradiation gave an important clue to an explanation as an increase in non-breast cancer–related mortality was seen only for patients treated in older trials and not in trials starting in 1989 or thereafter (15).

Our findings, based on a large and representative patient cohort, have important—reassuring—consequences for decision making concerning elective lymph node treatment in breast cancer. Still, the differences might be explained from progress in cardiology as well as by patient selection. The increase of 7.4% in the relative risk for major coronary events per Gray (Gy) as in the study of Darby et al. (21) was similar in women with and without cardiac risk factors at the time of treatment. Therefore, it seems logical to take the preexisting cardiac comorbidity of patients into consideration when weighting the assumed benefits against the possible risks, putting the threshold

for accepting a planned dose distribution at lower mean heart dose levels for those at higher baseline risks (3,4,19,21). Unfortunately, as our study was conducted before the era of routine Computed Tomography (CT)-based treatment planning, we cannot accurately estimate the cardiac doses delivered in the patients who participated in our trial. However, knowledge of possible risks might have guided patient selection towards women bearing a relatively low baseline risk and might have affected treatment planning. So, despite the long follow-up period in our trial, increased rates of side effects may eventually be found after even longer follow-up, as noted by others (3,4,19,23). Therefore, we advise that patients are properly informed during the shared decision-making process and that long-term follow-up for selected patients at higher risk for cardiovascular and pulmonary toxicity, including those treated before 1989—based on the EBCTCG data—and smokers should be encouraged.

Another important implication of our findings concerns the introduction of new techniques and preventive treatments for reducing the risks of cardiovascular morbidity and mortality. For example, the introduction of novel radiation therapy techniques suggest that, based on comparative dosimetry analyses, the heart and lung doses can be further reduced in the subgroup of patients with a challenging anatomy (24,25). However, contemporary techniques have evolved a lot over time, with a sharp decrease in cardiac doses compared with the past. This, combined with the low rates of side effects and the absence of excess non-breast cancer–related mortality in our study, challenges the validity of the model-based indication for proton therapy in breast cancer, which ultimately might be only beneficial in very specific circumstances (26). Overall, we expect that by lowering radiation exposure to the heart, the risk of cardiovascular morbidity and mortality will be further reduced, which may require actualization of the risk-estimates that are currently used (20). Moreover, cardiology has evolved a lot over the last decades, resulting in decreasing morbidity and mortality by preventive and therapeutic measures for cardiovascular events, which is similarly reflected by an improved awareness about the relevance of cardiac risk factors by general practitioners and patients. This ultimately leads to an improved efficacy of preventive and therapeutic interventions in patients at substantial risk for radiation-induced heart disease (20).

The risk of developing radiation-associated secondary cancers is well known, especially when combined with other risk factors such as smoking and, especially for younger women, at the contralateral breast (27–30). We did not observe an increase in contralateral breast cancer incidence in our study, although we could have expected more second cancers in the IM-MS arm due to the increased irradiated tissue volumes as such and the anatomical site of the esophagus and thyroid gland. We cannot exclude a small tumor-inducing effect because the absolute numbers are small and—in contrast to other studies—we did not compare irradiation vs no irradiation, with most patients receiving at least radiation therapy of the breast or the chest wall.

Among the strengths of our study are the high-quality data for a large number of patients during a very long follow-up period, the extensive quality assurance program linked to the trial, and the real international, multicentric contribution from a wide range of participants, increasing the applicability of the outcomes to clinical practice (31). The lack of detailed specification of events concerning side effects on the original CRF dating from 1992 was compensated by the supplementary, dedicated, late-effects CRF that was to be filled in every 5 years. This allowed for a more detailed analysis and, to some extent, for an innovative comparison between the conventional cumulative data that are annually collected during follow-up with a cumulative, 5-yearly, cross-sectional recording.

As limitations of our study, we include the lack of quality-of-life evaluations, the unbalanced amount of missing and "unknown" data between the treatment arms, and the use of radiation techniques during the accrual period spanning from 1996 until 2004 that are considered to be outdated by now (32). We expect that with contemporary volume-based radiation therapy, outcomes will be even better by improved coverage of target volumes, more homogeneous dose delivery, and decreased doses to nontarget tissues (19,21,24,33). The low rates of recorded side effects in our trial preclude any meaningful subgroup analysis for patient-, tumor-, and treatment-related factors with clinical impact. We assume that this will be further elucidated in the framework of the ongoing meta-analysis by the EBCTCG. Finally, a recorded side effect such as a transient radiation pneumonitis observed in a patient 1 year after treatment has the potential for full recovery, but this cannot be formally addressed and is complicated by patient attrition.

Overall, for patients treated 20 years ago, we demonstrated better cancer-related outcomes (73.1% overall survival rate at 15 years) combined with lower rates of side effects compared with those predicted by others (18,20,33,34). This challenges several assumptions about the critical balance between benefits and risks derived from radiation therapy for breast cancer, where both the relative calculated risk increment using data from other studies and the absolute baseline risk in the contemporary population are likely to be overestimated(35). Therefore, currently used risk estimations should be reviewed using contemporary data and details about outcomes for improved patient selection. We will continue follow-up for an additional 5 years, with an expected final analysis at 20 years follow-up in 2023.

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Data Availability

Data will be shared according to the EORTC data release policy (https://www.eortc.org/data-sharing/).

References

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014;383(9935):2127-2135.
2. Darby S, McGale P, Correa C, et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707-1716.
3. Cuzick J, Stewart H, Peto R, et al. Overview of randomized trials comparing radical mastectomy without radiotherapy against simple mastectomy with radiotherapy in breast cancer. *Cancer Treat Rep*. 1987;71(1):17-14.
4. Cuzick J, Stewart HJ, Peto R, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. *Recent Results Cancer Res*. 1988;111:108-129.
5. Harris JR, Hellman S. Put the "hockey stick" on ice. *Int J Radiat Oncol Biol Phys*. 1988;15(2):497-499.
6. Arriagada R, Lê MG, Mouriesse H, et al. Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. *Radiother Oncol*. 1988;11(3):213-222.
7. Arriagada R, Rutqvist LE, Mattsson A, et al. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. *J Clin Oncol*. 1995;13(12):2869-2878.
8. Early Breast Cancer Trialist's Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomised trials. *N Eng J Med*. 1995;333(22):1444-1455.
9. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med*. 1997;337(14):949-955.
10. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet*. 1999;353(9165):1641-1648.
11. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med*. 1997;337(14):956-962.
12. Poortmans PM, Collette S, Kirkove C, et al. EORTC Radiation Oncology and Breast Cancer Groups. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med*. 2015;373(4):317-327.
13. Whelan TJ, Olivotto IA, Parulekar WR, et al.; MA.20 Study Investigators. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373(4):307-316.
14. Thorsen LB, Offersen BV, Danø H, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol*. 2016;34(4):314-320.
15. Early Breast Cancer Trialists' Collaborative Group. Regional lymph node irradiation in early stage breast cancer: an EBCTCG meta-analysis of 13,000 women in 14 trials. Abstract GS4-02. Paper presented at the San Antonio Breast Cancer Symposium; December 2018; San Antonio, TX.
16. Poortmans PM, Weltens C, Fortpied C, et al. Fifteen-year results of the randomised EORTC trial 22922/10925 evaluating internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer. *Lancet Oncol*. 2020;21(12):1602-1610.
17. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368(11):987-998.
18. van den Bogaard VAB, Ta BDP, van der Schaaf A, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. *J Clin Oncol*. 2017;35(11):1171-1178.
19. Killander F, Anderson H, Kjellén E, et al. Increased cardio and cerebrovascular mortality in breast cancer patients treated with postmastectomy radiotherapy–25 year follow-up of a randomised trial from the South Sweden Breast Cancer Group. *Eur J Cancer*. 2014;50(13):2201-2210.
20. Jacobse JN, Duane FK, Boekel NB, et al. Radiation dose-response for risk of myocardial infarction in breast cancer survivors. *Int J Radiat Oncol Biol Phys*. 2019;103(3):595-604.
21. Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol*. 2015;114(1):3-10.
22. Bartlett FR, Donovan EM, McNair HA, et al. The UK HeartSpare Study (stage II): multicentre evaluation of a voluntary breath-hold technique in patients receiving breast radiotherapy. *Clin Oncol (R Coll Radiol)*. 2017;29(3):e51-e56.
23. Lorenzen EL, Rehammar JC, Jensen MB. Ewertz M, Brink C. Radiation-induced risk of ischemic heart disease following breast cancer radiotherapy in Denmark. 1977-2005. *Radiother Oncol*. 2020;152:103-110.
24. Ranger A, Dunlop A, Hutchinson K, et al. A dosimetry comparison of breast radiotherapy techniques to treat locoregional lymph nodes including the internal mammary chain. *Clin Oncol (R Coll Radiol)*. 2018;30(6):346-353.
25. Maduro JH. Future options: the potential role of proton irradiation. *Breast*. 2019;48(suppl 1):S76-S80.
26. Osman SO, Hol S, Poortmans PM, Essers M. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. *Radiother Oncol*. 2014;112(1):17-22.
27. Grantzau T, Thomsen MS, Væth M, et al. Risk of second primary lung cancer in women after radiotherapy for breast cancer. *Radiother Oncol*. 2014;111(3):366-373.
28. Taylor C, Correa C, Duane FK, et al.; for the Early Breast Cancer Trialists' Collaborative Group. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol*. 2017;35(15):1641-1649.
29. Aznar MC, Duane FK, Darby SC, et al. Exposure of the lungs in breast cancer radiotherapy: a systematic review of lung doses published 2010-2015. *Radiother Oncol*. 2018;126(1):148-154.

30. Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: a systematic review and meta-analysis of population-based studies including 522,739 patients. *Radiother Oncol*. 2016;121(3):402-413.
31. Poortmans P, Kouloulias V, van Tienhoven G, et al.; EORTC Radiation Oncology and Breast Cancer Groups. Quality assurance in the EORTC randomized trial 22922/10925 investigating the role of irradiation of the internal mammary and medial supraclavicular lymph node chain works. *Strahlenther Onkol*. 2006;182(10):576-582.
32. Lievens Y, Poortmans P, Van den Bogaert W. A glance on quality assurance in EORTC study 22922 evaluating techniques for internal mammary and medial supraclavicular lymph node chain irradiation in breast cancer. *Radiother Oncol*. 2001;60(3):257-265.
33. Maas AH, Ottevanger N, Atsma F, et al. Cardiovascular surveillance in breast cancer treatment: a more individualized approach is needed. *Maturitas*. 2016; 89:58-62.
34. Roos CTG, van den Bogaard VAB, Greuter MJW, et al. Is the coronary artery calcium score associated with acute coronary events in breast cancer patients treated with radiotherapy? *Radiother Oncol*. 2018;126(1):170-176.
35. Raphael DB, Ter Stege JA, Russell NS, et al. What do patients and health care professionals view as important attributes in radiotherapy decisions? Input for a breast cancer patient decision aid. *Breast*. 2020;49:149-156.