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Clinical Investigation: Breast Cancer

Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy

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Summary

This randomized trial evaluated the role of internal mammary nodes (IMN) irradiation after mastectomy for pN0/pN1 internal tumors or pN1 external tumors. A total of 1334 patients were included in the analysis, with a median follow-up of 11.3 years. No benefit could be demonstrated for IMN irradiation: 10-year survival

Purpose: To evaluate the efficacy of irradiation of internal mammary nodes (IMN) on 10-year overall survival in breast cancer patients after mastectomy.

Methods and Patients: This multicenter phase 3 study enrolled patients with positive axillary nodes (pN+) or central/medial tumors with or without pN+. Other inclusion criteria were age <75 and a Karnofsky index ≥ 70. All patients received postoperative irradiation of the chest wall and supraclavicular nodes and were randomly assigned to receive IMN irradiation or not. Randomization was stratified by tumor location (medial/central or lateral), axillary lymph node status, and adjuvant therapy (chemotherapy vs no chemotherapy). The prescribed dose of irradiation to the target volumes was 50 Gy or equivalent. The first 5 intercostal spaces were included in the IMN target volume, and two-thirds of the dose (31.5 Gy) was given by electrons. The primary outcome was overall survival at 10 years. Disease-free survival and toxicity were secondary outcomes.

Results: T total of 1334 patients were analyzed after a median follow-up of 11.3 years among the survivors. No benefit of IMN irradiation on the overall survival could be

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rates were 59.3% and 62.6% in the IMN− and IMN+ groups, respectively.

demonstrated: the 10-year overall survival was 59.3% in the IMN-nonirradiated group versus 62.6% in the IMN-irradiated group ($P=.8$). According to stratification factors, we defined 6 subgroups (medial/central or lateral tumor, pN0 [only for medial/central] or pN+, and chemotherapy or not). In all these subgroups, IMN irradiation did not significantly improve overall survival.

Conclusions: In patients treated with 2-dimensional techniques, we failed to demonstrate a survival benefit for IMN irradiation. This study cannot rule out a moderate benefit, especially with more modern, conformal techniques applied to a higher risk population.

Introduction

Some randomized trials have demonstrated that postoperative radiation therapy (RT) increased survival after mastectomy (1-3). A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCCTCG) has confirmed that postmastectomy irradiation in node-positive (pN+) patients decreased the rate of local control failures from 23% to 6%, with a survival gain of 5.4% (4). After mastectomy, locoregional relapses were mainly located on the chest wall, then in the supraclavicular and axillary areas. The rate of clinical relapse in internal mammary nodes (IMN) was low, approximately 1% (5).

In the randomized trials that demonstrated benefits from postmastectomy irradiation, the chest wall and nodal areas, including IMN, were all irradiated. The IMN involvement was demonstrated by historical surgical series and was more often observed in cases of positive axillary nodes or medial tumor location (6). Although cancer recurrence in the IMN is rare, one cannot exclude an increased rate of metastatic disease due to secondary seeding from persistent disease. However, a large cooperative randomized trial demonstrated no benefit from surgical dissection of the IMN (7, 8), and the few retrospective series (9-11) reported only conflicting results regarding the role of IMN irradiation.

Some large epidemiologic studies with long follow-up periods have shown that postoperative RT is associated with an increased incidence of cardiac mortality (12-14). In the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database, the rate of death from heart disease was higher in women treated for left breast cancer than for those with right breast cancer (13.1% vs 10.2%, respectively); however, this difference was no longer significant for women treated after 1980 (13, 15). Also, in the Danish study (16), no increase in cardiac deaths was observed. This may be the result of improvements in radiation techniques, particularly the use of electrons, but also of shorter follow-ups, because cardiac mortality did not significantly increase before 12-15 years after cancer (17).

Nevertheless, irradiation of IMN may be an important risk factor in regard to this cardiac toxicity. Even with a separate anterior field and more than 80% of the dose given by electrons, the dose to the heart is not negligible (18). In a retrospective analysis, the risks of coronary heart disease and of myocardial infarction were significantly associated with IMN irradiation (7% vs 18%, $P<.001$ and 3% vs 9%, $P=.01$, respectively) (19). An epidemiologic Dutch study showed a statistical correlation between IMN irradiation and cardiovascular events (20).

The purpose of the present prospective randomized trial was to compare the 10-year overall survival of patients who received IMN radiation after postmastectomy with that of patients who did not.

Methods and Materials

Study population

From January 1991 to December 1997, 1407 pre- and postmenopausal women with newly diagnosed stage I or II adenocarcinoma of the breast were enrolled in the study after undergoing a modified radical mastectomy with the following inclusion criteria: positive axillary nodes or a medial/central tumor with or without axillary lymph node involvement.

Other inclusion criteria included tumor size larger than 1 cm, age <75 years, ≥70% Karnofsky performance scale, no bilateral breast cancer, no history of cancer or severe comorbidity, and no evidence of metastatic disease as determined by physical examination, chest radiography and bone scintigraphy.

Study design

The study was designed as a multicenter randomized trial that involved 13 French participating centers (see list in the Supplemental Appendix). It was approved by the Hospital Ethical Committee and conducted in accordance with the Helsinki Declaration of 1975 on human experimentation. After patients gave written informed consent, they were randomly assigned by the coordinating center to 1 of 2 groups: the internal mammary chain irradiation group (IMN-RT+) or the internal mammary chain no-irradiation group (IMN-RT−). The primary outcome was 10-year overall survival. Secondary outcomes were disease-free and toxicity-free survival, particularly cardiac toxicity. Acute myocardial infarction, other ischemic heart disease, and congestive heart failure were considered cardiac events. However, in designing this trial, we believed that some subgroups could benefit from IMN irradiation more than others: so, from the beginning of the study, we planned a subgroup analysis according to 3 known prognostic factors and stratified the population based on those factors. The randomization was stratified by tumor location (medial/central vs lateral), axillary lymph node status (pN0 vs pN+), and use of adjuvant therapy (chemotherapy vs no chemotherapy).

Surgery and histopathology analysis

All patients underwent a modified radical mastectomy, with axillary node dissection of levels I and II. A histopathology examination of at least 3 lymph nodes was required. No IMN