

## Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer

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### Abstract

*Background and purpose:* Some types of radiation therapy have been associated with an increased risk of cardiac mortality and morbidity in patients with early-stage breast cancer. A relationship has been observed between cardiac radiation dose-volume and the level of excess risk of cardiac mortality. However, relatively few data are available on the morbidity from myocardial infarction associated with adjuvant radiotherapy.

*Patients and methods:* From 1971 to 1976, a total of 960 patients with operable breast cancer were randomly allocated to preoperative radiation therapy, postoperative radiation therapy or to surgery alone. A previous analysis of the cardiac dose-volumes with the treatment techniques used in the trial indicated that the irradiated patients could roughly be divided into three groups. Information on the number of myocardial infarctions was obtained through computerized record linkage with a population-based registry of myocardial infarctions in Stockholm County. Information on cause-specific mortality was obtained from the Swedish Cause-of-Death Registry. The median follow-up was 20 years (range 17–23 years).

*Results:* A total of 58 patients developed an acute myocardial infarction during the period of follow-up. The number of myocardial infarction cases was not significantly different between the three treatment groups. When analyzed according to estimated cardiac radiation dose-volumes, patients in the highest dose-volume subgroup exhibited a hazard of myocardial infarction of 1.3 (95% CI 0.7–2.6) relative to that of the surgical controls, whereas the corresponding relative hazard for the intermediate and low dose-volume subgroups was below unity. Data on death due to cardiovascular disease showed that patients in the high dose-volume group exhibited a hazard of 2.0 (95% CI 1.0–3.9,  $P=0.04$ ) relative to that of the surgical controls. Concerning death due to ischemic heart disease, the relative hazard for the same subgroup was 2.5 (95% CI 1.1–5.7,  $P=0.03$ ). The difference between the groups was established after 4–5 years. The cumulative incidence curves continued to diverge up to about 10–12 years. No further divergence appeared after 12 years, but the number of events was low.

*Conclusions:* This analysis confirms and extends previous results from the trial. Cardiac mortality was positively correlated with the cardiac dose-volume. Patients receiving high dose-volumes exhibited an increased mortality of ischemic heart disease, but not of myocardial infarction, which implies another mechanism, e.g. radiation-induced microvascular damage to the heart.