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Original Research

No breast cancer subgroup can be spared postoperative radiotherapy after breast-conserving surgery. Fifteen-year results from the Swedish Breast Cancer Group randomised trial, SweBCG 91 RT

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Abstract ***Background:*** Breast-conserving surgery (BCS) followed by radiotherapy (RT) is an established treatment for women with T1-2N0 breast cancers. Since subgroups of patients have low ipsilateral breast tumour recurrence (IBTR) rates, it is important to study whether RT is necessary for all patients.

Patients and methods: A total of 1187 women with primary T1-2N0M0 breast cancer were randomised, after standardised sector resection, to postoperative whole breast RT or no local treatment. Adjuvant systemic therapy was offered to patients with stage II cancers. Patients were followed with clinical examinations and annual mammography for 10 years and thereafter referred to the Swedish mammography screening program.

Results: After 15 years of follow-up, a higher cumulative incidence of IBTR was observed in control patients, 23.9%, versus irradiated patients, 11.5%, $P < 0.001$. Recurrence-free survival was inferior, 51.7% versus 60.4%, $P = 0.0013$. The main effect of RT was seen during the first 5 years. However, overall survival was not significantly lower 68.4% versus 71.1%, $P = 0.68$,

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nor was breast cancer–specific mortality significantly higher.
Conclusions: RT after BCS significantly reduced the incidence of IBTR at 15 years of follow-up. We were unable to identify subgroups which could be spared RT. Breast cancer mortality was not significantly reduced after RT. Good predictive markers for radiation sensitivity and improved adjuvant systemic therapy are needed to omit RT after BCS.

1. Introduction

The majority of patients with primary breast cancer are treated with breast-conserving surgery (BCS) followed by radiotherapy (RT). The use of breast preservation can be expected to increase with more frequent use of neoadjuvant systemic therapy [1].

The importance of reducing ipsilateral breast tumour recurrences (IBTRs) by postoperative RT has been demonstrated in two meta-analyses from the Early Breast Cancer Trialists' Collaborative group (EBCTCG) [2,3]. The latest meta-analysis from 2011 concluded that about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10. Significant reductions of mortality were reported for patients with high-risk lymph node–negative breast cancer and for patients with lymph node–positive breast cancer, i.e., patients with a 10-year risk of recurrence above 15% without RT [3]. However, the majority of individual trials of breast-conserving therapy with or without RT were unable to demonstrate improved survival after RT [4,5].

As the majority of breast cancers do not recur locally, even in the absence of RT, much effort has been spent trying to identify patients for whom postoperative RT can be omitted [6–13]. A previous Swedish trial of BCS with and without RT also demonstrated a significant reduction of local recurrences but no reduction of breast cancer mortality [14] and that study was the forerunner off the present larger randomised trial on a national basis, Swedish Breast Cancer Group 91 RT (SweBCG 91 RT).

The aim of the present trial was to study whether postoperative RT is necessary for all patient subgroups in the setting of a nation-wide mammography screening program. Results of this trial with the 5-year follow-up were published in 2003 [15]. A gene expression signature for resistance to RT has also been defined from this patient material [16]. Late side effects of RT in this trial have also been reported [17,18].

2. Patients and methods

2.1. Study design

This trial, including inclusion criteria, was described in detail previously [15]. A total of 1187 patients, below 76 years, with T1-2N0M0 primary, invasive breast cancer were randomised from 1991 to 1997 to postoperative RT or no further treatment after a standardised radical sector resection and axillary dissection of levels I and II [19]. Randomisation was done by telephone calls to the three regional cancer registries. The patients were stratified according to operating hospital and mode of detection, screening versus not. The randomisation offices were located outside of the clinical units, and the size of the blocks was unknown to the participating clinicians. A CONSORT diagram of the SweBCG 91 RT trial is shown in Fig. 1. RT with tangential opposed fields of 4–6 MV photons, 48–54 Gy in 24–27 fractions, was administered to the remaining breast parenchyma. Doses were specified according to the International Commission on Radiation Units & Measurements [20]. For all patients, individual computerised dose planning with wedge compensators was used. Three-dimensional dose planning on multiple CT slices 10 mm apart was used for 69% of the patients. For the remaining patients, two dimensional planning based on three CT slices was used. Adjuvant systemic therapy was not regulated by the study protocol but was prescribed for stage II patients according to regional treatment guidelines. Of 1178 eligible patients (Fig. 1), 1072 received no adjuvant systemic therapy, 84 patients were treated with tamoxifen and 22 received cyclophosphamide/methotrexate/5-fluorouracil chemotherapy (CMF). Patients were followed annually with clinical examination and mammography for 10 years. Thereafter, they were referred to the Swedish nation-wide breast screening program which comprises women 50–75 years of age with examination every 18–24 months depending on age. After 15 years, all case records have been reviewed. Follow-up was also done by linkage to the Swedish Cause of Death Registry and the Swedish population registry. Forty-eight patients, 23 in the RT and 25 in the control group, were lost to follow-up between years 5 and 15 and thus did not contribute to follow-up after 5 years except for vital status. The reason was that they were followed in private practices, and their charts could not be monitored. No other patients were lost to follow-up. Median follow-up for patients alive and recurrence-free was 15.6 years. The trial was approved by the Ethics committee, and oral informed consent was obtained from all patients.