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Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: a randomised clinical trial in a population with access to public mammography screening

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Abstract

The effect of postoperative radiotherapy after sector resection for stage I-II lymph node-negative breast cancer was evaluated in a patient population with access to public mammographical screening. 1187 women were randomised to no further treatment or postoperative radiotherapy following a standardised sector resection and axillary dissection. Radiation was administered to a dose of 48-54 Gy. Median age was 60 years, and median size of the detected tumours was 12 mm. Of the women 65% had their tumours detected by mammographical screening. The relative risk (RR) of ipsilateral breast recurrence was significantly higher in the non-irradiated patients compared with the irradiated patients, RR = 3.33 (95% Confidence Interval (CI) 2.13–5.19, $P < 0.001$). The corresponding cumulative incidence at 5 years was 14% versus 4%, respectively. Overall survival (OS) was similar, RR = 1.16 (95% CI 0.81–1.65, $P = 0.41$), with 5 year probabilities of 93 and 94%, respectively. Recurrence-free survival (RFS) at 5 years was significantly lower in the non-irradiated women, 77% versus 88% ($P < 0.001$). Although women above 49 years of age, whose tumours were detected with mammographical screening, had the lowest rate of ipsilateral breast recurrence in this study, the cumulative incidence of such event amounted to 10% at 5 years if radiotherapy was not given. Such a recurrence rate has been considered as unacceptably high, but is, however, in the same range as that reported after lumpectomy and postoperative radiotherapy in published series.

Keywords: Radiotherapy; Breast conservation surgery; Sector resection; Randomised trial; Breast recurrence; Mammographical screening; Lymph node-negative breast cancer

1. Introduction

Breast conservation surgery (BCS) with postoperative radiotherapy (RT) has become standard treatment for early breast cancer [1–3]. The first randomised trial, that studied the feasibility of omitting RT after BCS was published in 1985 [2]. The Uppsala-Örebro multicentre trial of breast conservation, with and without RT, reported early results in 1990 [4]. With a median follow-up of 3 years, no significant difference in risk of ipsilateral breast recurrence could be demonstrated. These

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results and the simultaneous introduction of public mammographical screening in Sweden was the basis for a new Swedish Breast Cancer Group (SweBCG) multicentre study. The aim was to study, in a broader patient series, the effect of postoperative RT after standardised BCS. Thus, the present study has a more extensive geographical coverage and wider patient inclusion criteria than the Uppsala-Örebro trial.

2. Patients and methods

2.1. Trial design

In this multi-institutional trial women with stage I-II lymph node-negative breast cancer were randomised to postoperative RT or no further local treatment after BCS. The primary aim was to study if local tumour control could be obtained by standardised sector resection and axillary dissection without postoperative RT. Secondary aims were to compare overall and recurrence-free survival, to study whether patients with a high or low risk of recurrence could be identified at the primary operation, frequency of mastectomy, and if postoperative RT would increase the incidence of contralateral breast cancer. In addition, the influence of tumour detection by mammographical screening on the risk of local recurrence was to be analysed.

Patients were randomised in permutated blocks of 8 by telephone calls to three regional oncological centres, and were stratified by the randomising department and whether they were detected by mammographical screening or not. The randomising offices were located outside of the clinical units and the size of the blocks was unknown to the participating clinicians. Thus, the allocation scheme was concealed from the clinicians who entered patients into the trial.

The trial was approved by the regional ethics committees in the three participating healthcare regions: Uppsala-Örebro, West Sweden and South Sweden. Oral informed consent was obtained from all of the patients.

2.2. Eligibility criteria

Women below 76 years with clinically- or screening-detected invasive lymph node-negative breast cancers stage I and II, and operated upon with BCS and axillary dissection were eligible. Patients with multifocal tumours located in the same quadrant of the breast were included, provided that the distance between invasive cancers or cancers *in situ* was less than 21 mm. Previous treatment for contralateral breast cancer was allowed if the patient was without signs of recurrent breast cancer.

Using the regional breast cancer registries, we also identified all patients that fulfilled age and tumour size criteria in South and West Sweden during the trial period.

2.3. Surgery

Surgery was performed as a standardised sector resection previously described in Ref. [5], and axillary dissection of levels one and two. In short, the mammary gland was dissected in the plane of Scarpa's fascia down to the pectoralis major muscle. The pectoral fascia was included in the operative specimen and a sector around the tumour encompassing the periphery of the gland was carried out. Excision of an eclipse of overlying skin was optional. A palpable-free margin of at least 1 cm around the tumour was aimed for. Radical excision, defined as no tumour cells in the margins of the resected specimen, was required. Microscopic examination of at least five lymph nodes was recommended. Non-palpable lesions were localised with the use of a wire-hook technique or stereotactic application of dye. Perioperative radiography of the operative specimen was mandatory to ensure that non-palpable lesions were completely removed.

2.4. Radiotherapy and adjuvant medical treatment

Irradiation was administered as tangential opposing beams with 4–6 MeV photons. Treatment was given 4 or 5 days a week over 5 weeks to a total target dose of 48 Gy in West Sweden, 50 Gy in South Sweden, or 54 Gy in the Uppsala-Örebro region. Dose was specified at the intersection point of the opposing tangential beams or at the centre of the clinical target volume defined as remaining breast parenchyma according to the International Commission on Radiation Units and Measurements [6]. Individual dose planning was performed for all patients. Computer-based three-dimensional dose planning (Helix AB) in multiple sections through the breast was done for patients treated at the departments of radiotherapy in South Sweden and one radiotherapy department in West Sweden, i.e. 69% of all patients included in the study. No boost therapy was given.

Adjuvant medical treatment was not regulated by the protocol. Breast cancer management programmes in the participating healthcare regions did not recommend adjuvant treatment for lymph-node negative patients with stage I tumours, but this was recommended for some patients with tumours above 2 cm.

2.5. Follow-up and evaluation

Follow-up consisted of yearly visits with physical examination and mammography. Patient data were collected at each visit and entered into the breast cancer register at each of the three participating oncology centres. In addition, during 1999, all patient data in the patient's original hospital records, as well as operation reports, were independently monitored. Vital status was checked with national Swedish population and cause of death registers. End of follow-up was 28 February 1999,

for all types of events except death of any cause. For this event, patients were followed until 31 August 2000.

2.6. Statistics

The primary endpoint of the study was ipsilateral breast recurrence. Secondary endpoints were (1) overall survival (OS), (2) recurrence-free survival (RFS: i.e. time to the first of the events, ipsilateral breast recurrence, regional and distant recurrence and death), (3) breast cancer death, and (4) contralateral breast cancer. The study was dimensioned to be able to detect an increase in 5-year ipsilateral breast recurrence rate from 5% in the radiotherapy arm to 9% in the surgery only arm, with a power of 80% using a one-sided test with a significance level of 5%. A rate of ineligibility of 5% was assumed. This yielded a total of 1100 patients.

Cumulative incidence curves [7] were used for ipsilateral breast recurrence as the first event in the presence of other recurrences and death. This method was also used to determine the cumulative incidence of mastectomy at local recurrence, with death as a competing event. Cumulative incidence curves estimate observable probabilities and are preferred when the event under interest competes in time with other events [8]. Kaplan–Meier curves were used to illustrate RFS and OS. Log-rank tests and Cox regression analyses, stratified for healthcare region and screening detection, were used to compare event rates between the treatment groups. When evaluating the prognostic effect of screening detection, the analyses were stratified for region and treatment group.

According to the dimensioning of the study, the test of the primary hypothesis should be done with a one-sided test in order to demonstrate that surgery without RT increases the local recurrence rate compared with surgery with RT. Since the inception of the study in the late 1980s, a number of studies have shown that this is the case. It is thus important to determine both upper and lower confidence limits for relative and absolute risks when RT is not added. Therefore, all confidence intervals and significance tests are two-sided. Moreover, all analyses were done according to the intention-to-treat principle [9].

3. Results

3.1. Patient and tumour characteristics

From January 1991 to September 1997, 1187 patients were randomised in the study. In the Uppsala-Örebro region, the study was terminated after 8 months and 43 randomised patients due to low acceptance among clinical investigators. In South and West Sweden, 31% of all women with lymph node-negative breast cancer fulfilling tumour size and age criteria during the study period were included. 594 women were randomised to no further treatment, and 593 to postoperative RT. 7 in the control group were irradiated, and 27 women in the RT arm were not given RT. No patient was lost to follow-up. 6 patients were 76–77 years of age and thus above the age limit for inclusion. These patients were not excluded, as they were not considered to be biologically different from patients aged 70–75 years. 9 patients were excluded due to major violations of entry criteria: 2 with lymph node metastases, 5 with non-invasive cancer (i.e. ductal carcinoma *in situ*; (DCIS)), and 2 patients who were operated upon primarily with a modified radical mastectomy. The remaining 1178 patients were included in the analyses (Fig. 1).

Patient and tumour characteristics were well balanced between the treatment arms (Table 1). Median age was 60 years, and 65% of the tumours were detected using mammographical screening. Median size of the tumours was 12 mm, and a median of 11 lymph nodes from the

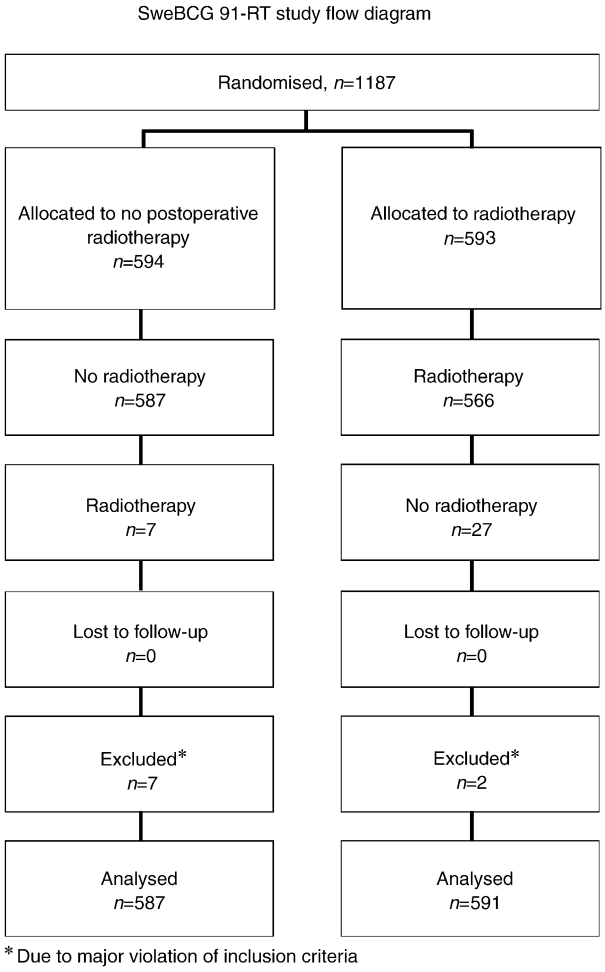

Fig. 1. Study flow diagram the for SweBCG 91-RT trial of breast conservation surgery, with and without radiotherapy (RT).

Table 1
Patients' and tumour characteristics in 1178 patients randomised to sector resection, without and with postoperative radiotherapy

	Control	Radiotherapy
Number of patients	587	591
Age, years		
Median (range)	60 (32–78)	60 (31–78)
⩽39	15	9
40–49	108	93
50–59	169	190
60–69	225	227
⩾70	70	72
Menopausal status		
Pre-	123	109
Post-	450	469
Unknown	14	13
Detected by screening mammography	383	386
Tumour size (mm)		
Median (range)	12 (1–40)	12 (2–50)
⩽10	232	243
11–20	301	299
21–30	53	48
⩾31	1	1
Oestrogen receptor status		
Positive	338	334
Negative	74	78
Unknown	175	179
Progesterone receptor status		
Positive	290	282
Negative	121	130
Unknown	176	179
Number of examined lymph nodes		
Median (range)	11 (0–56)	11 (1–41)

removed axillary specimens was examined. Using haematoxylin-eosin staining, no metastatic tumour cells were detected in the axillary lymph nodes. 57% of all tumours were classified as oestrogen receptor-positive.

3.2. Radiotherapy, adjuvant medical treatment and follow-up

The median interval from operation to start of radiotherapy was 2.4 months (range 1.1–7.2 months), and the median administered dose was 50 Gy (range 42–58 Gy). 99% of the patients received doses between 48 and 54 Gy. Of oestrogen receptor-positive patients, 47 in the surgery only group and 36 in the irradiated group were treated with tamoxifen. Among oestrogen receptor-negative premenopausal women, 12 patients in each group received chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil.

Median follow-up time for recurrence was 61 months (range 10–98 months) and for survival 85 months (range 36–116 months) for those who did not experience an event.

3.3. Ipsilateral breast recurrence and other first events

In the surgery only versus the RT group, there were 78 versus 26 ipsilateral breast recurrences, six versus three axillary recurrences, and 25 vs. 23 patients with distant metastases as a first event. 18 versus 20 patients died from causes other than breast cancer (Table 2). The relative risk (RR) of ipsilateral breast recurrence as a first event was significantly higher (RR = 3.33, 95% Confidence Interval (CI) 2.13–5.19, $P < 0.001$) in the non-irradiated group compared with the irradiated patients. The 5-year cumulative incidences were 14% (95% CI 11–19%) and 4% (95% CI 3–7%), respectively (Fig. 2). First events other than ipsilateral breast recurrence at 5 years did not differ between the two groups: 5% (95% CI 3–8%) versus 4% (95% CI 2–6%).

Ipsilateral breast recurrences were localised in the same quadrant as the previous tumour and of the same histological type in 90% of the patients. Of recurrences, 10% were DCIS and 90% invasive carcinomas.

Treatment for relapse was mastectomy in 70% and another sector resection in 30%. The cumulative incidence of ipsilateral mastectomy at 5 years was 10% (95% CI 7–14%) in the control group and 4% (95% CI 2–6%) in the irradiated group ($P < 0.001$).

Table 2
First events in 1178 patients with lymph node-negative breast cancer randomised to sector resection, without and with postoperative radiotherapy

	Control $n = 587$	Radiotherapy $n = 591$
Ipsilateral breast recurrence	78	26
Axillary recurrence	6	3
Distant metastases	25	23
Non-breast cancer deaths	18	20

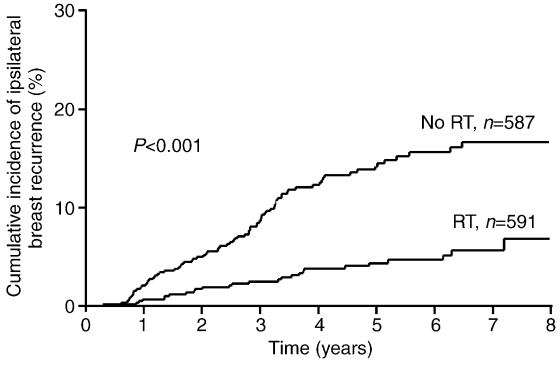

Fig. 2. Cumulative incidence of ipsilateral breast recurrence as a first event in 1178 patients after sector resection for lymph node-negative breast cancer. 587 patients were randomised to no further treatment (78 recurrences), and 591 to postoperative radiotherapy (26 recurrences).

3.4. Overall survival, breast cancer death, and RFS

Similar survival rates were observed (RR = 1.16, 95% CI 0.81–1.65, $P = 0.41$) between non-irradiated and irradiated patients; the 5 year OS rates were 93% versus 94%, respectively (Fig. 3). The cumulative incidence of breast cancer death at 5 years was also similar in the two groups, 5 versus 4 percent, respectively. RFS was, due to the larger number of ipsilateral breast recurrences, worse in the surgery only group compared with the RT group (RR = 1.94, 95% CI 1.46–2.60, $P < 0.001$). The 5-year RFS rates were 77 versus 88%, respectively (Fig. 4).

3.5. Influence of screening detection and age on ipsilateral breast recurrence

The risk of ipsilateral breast recurrence was lower for screening-detected compared with clinically-detected breast cancers (RR = 0.62, 95% CI 0.42–0.91, $P = 0.015$).

Among non-irradiated patients, the 5-year breast recurrence cumulative incidence was 11% (95% CI, 8–16%) and 19% (95% CI, 12–30%) among screening- and clinically-detected women (Fig. 5). The corresponding figures for the irradiated patients were 4% (95% CI 2–7%) and 5% (95% CI 3–10%). There was a highly significant difference comparing all four groups, $P < 0.001$ (Fig. 5).

To study the effect of age on the ipsilateral breast recurrence rate, indicator variables were constructed for the age classes 30–49, 50–59, 60–69 and 70–79 years. Using Cox regression analysis, stratified for treatment group, healthcare region and screening detection, it was found that the effect from all age classes above 49 years was similar; the relative risk for the combined age groups, 50–79 years, was 0.62 (95% CI 0.39–0.96, $P = 0.034$) compared with younger women.

Fig. 6 shows the cumulative incidence of ipsilateral breast recurrence by treatment arm and age below or above 50 years. For non-irradiated women, the values at 5 years were 13% (95% CI 9–17%) for women 50 years or above and 20% (95% CI 12–35%) for women below 50 years. A combination of age above 49 years and screening detection identified a group among non-irradiated patients with a somewhat lower cumulative incidence at 5 years, 10% (95% CI, 7–15%). There was a highly significant difference comparing the four groups, $P < 0.001$.

3.6. Contralateral breast cancer

During the follow-up, contralateral breast cancer was diagnosed in 19 patients in the surgery only group and 20 in the RT group. The distribution of these contralateral cancers in the breast did not differ from that of the original tumours.

4. Discussion

The present study demonstrated a reduction in the cumulative incidence of ipsilateral breast recurrence at 5 years of follow-up from 14% to 4% due to the addition of external beam radiotherapy after a standardised sec-

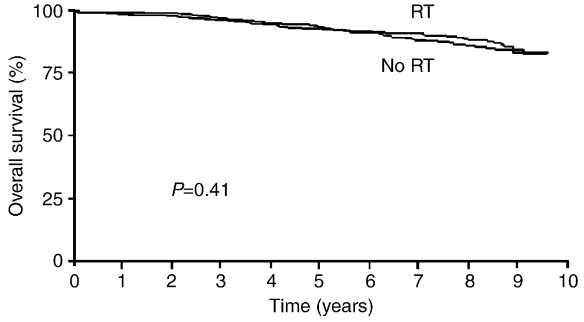

Fig. 3. Overall survival after sector resection for lymph node-negative breast cancer of 1178 patients randomised to no further treatment ($n = 587$), or postoperative radiotherapy ($n = 591$).

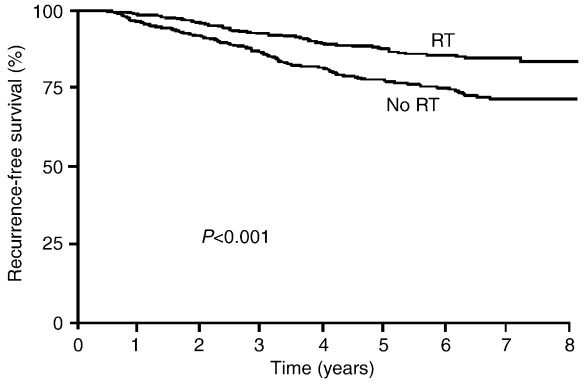

Fig. 4. Recurrence-free survival after sector resection for lymph node-negative breast cancer of 1178 patients randomised to no further treatment ($n = 587$), or postoperative radiotherapy ($n = 591$).

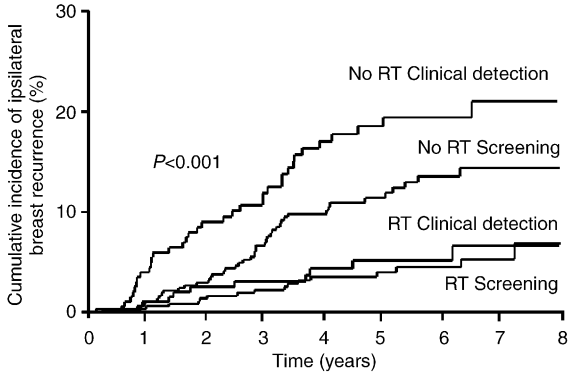

Fig. 5. Cumulative incidence of ipsilateral breast recurrence as first event after sector resection for lymph node-negative breast cancer in non-irradiated patients detected clinically ($n = 204$), or by mammographical screening ($n = 383$), and irradiated patients detected clinically ($n = 205$), or by mammographical screening ($n = 386$).

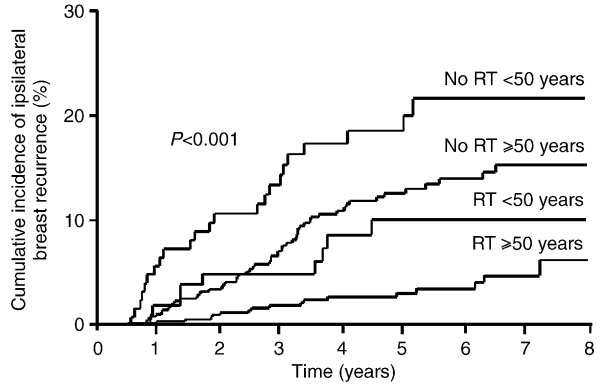

Fig. 6. Cumulative incidence of ipsilateral breast recurrence as a first event after sector resection for lymph node-negative breast cancer in non-irradiated patients below 50 years of age ($n=123$), or older ($n=464$), and irradiated patients below 50 years of age ($n=102$), or older ($n=489$).

tor resection and axillary dissection. In this trial, 31% of all patients in the regional breast cancer registries fulfilling tumour size and age criteria were included, 65% of all tumours were screening-detected, and the median size of the treated tumours was 12 mm.

The beneficial effect of RT is comparable to that of five previous randomised trials of postoperative RT reported after the initiation of this trial [10–15]. The RT doses administered in these trials were roughly similar (40–50 Gy to the whole breast parenchyma and with the addition of a 10–15 Gy boost to the scar area in three of the trials). However, surgical techniques varied from lumpectomy [2,12–15] to more extensive surgery such as sector resection [16] or quadrantectomy [17]. The reported recurrence rates after lumpectomy without RT at 5 years were higher, 18–35%, compared with more extensive surgery, 14–19%. A direct comparison of lumpectomy and more extensive surgery, quadrantectomy, has been done in only one randomised trial by the Milan group. Both treatment arms were given postoperative RT, and a significantly higher breast recurrence rate was seen after lumpectomy compared with quadrantectomy [18].

Comparing the RT arms in studies with lumpectomy and more extensive surgery, there is an indication of higher risks of recurrence at 5 years after lumpectomy (5.8–13.0%), [2,12–15] compared with more extensive surgery (2.3–4.0%) [16,17]. Irrespective of the type of surgery, no individual trial could demonstrate any detrimental effect on OS following the omission of RT [2,12–17]. Additionally, when all studies were combined in the previous overview of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995 [19] no survival benefit with postoperative RT was seen.

The outcome of this trial compares well with the results of previous Swedish studies on breast conservation. The risk of breast recurrence after postoperative RT reported in the Swedish observational study on 4500 patients treated from 1981 to 1990, 7.5% at 5 years, was higher than that of our randomised trial [20]. This is in agreement with the fact that the outcome of patients included in randomised trials is often more favourable than of patients treated outside of clinical protocols. Breast recurrence rates were also closely similar to those of the previous Uppsala-Örebro trial, despite wider inclusion criteria and patients being operated upon at 33 different hospitals [16,21].

For patients with hormone receptor-positive tumours, the use of tamoxifen resulted in a significant reduction of ipsilateral recurrence in addition to the protection given by postoperative RT as shown by the Stockholm Breast Cancer Group and National Surgical Adjuvant Breast Project (NSABP) [22,23]. From 1990, when this study was initiated, to 1995, women with lymph-node-negative breast cancer below two centimetres were not given adjuvant treatment. Therefore, only few women were exposed to adjuvant medical treatment and its effect on breast recurrence could not be analysed.

Our trial showed that in the present patient population, postoperative RT is generally indicated. All subsets of patients benefited from radiotherapy. A 20 year follow-up has clearly demonstrated the safety of this approach [24,25].

However, the breast recurrence rate in non-irradiated women was substantially lower in screening-detected compared with clinically-detected patients and thus the absolute benefit of radiotherapy was lower. Most patients treated with BCS without RT do not experience a breast recurrence. Thus, radiotherapy is over-treatment in this group of patients. It is therefore of importance to identify subgroups of patients with recurrence rates sufficiently low to make RT unjustified. In most of the previous trials this was not possible. However, in trials where surgery was performed as sector resection or quadrantectomy, reduced risks were reported for older patients, patients with small tumours and certain histologies [26,27].

Two trials have focused on patients operated upon with a lumpectomy with a low recurrence risk, a Finnish randomised radiotherapy trial, and an American prospective observational study. The purpose of the Finnish trial was to demonstrate no significant difference between the irradiated and non-irradiated patients [14]. In the study by Schnitt and colleagues, a recurrence rate below 1% per year was considered acceptable [28]. Neither of these goals was attained. Moreover, the recurrence rates in irradiated patients treated with lumpectomy have consistently been above 1% per year, with 5–10 years of follow-up. In our study, the lowest risk in non-irradiated patients was found for women above 49 years of age whose tumours were detected by mammographical screening. Their cumulative incidence rate at 5 years was 10%, which was deemed unacceptably high in the above-mentioned studies. Due to

the differences between patient populations entered into trials, comparisons between trials have limitations, but, nevertheless, this figure is in the same range, 5.8–13%, as that reported after lumpectomy and postoperative RT in previously published studies [2,12–17,23,29]. Since recurrence rates in this range after less extensive surgery, lumpectomy, and postoperative RT are considered acceptable, it could be argued that for selected patients more extensive surgery, such as sector resection, without postoperative RT may be a possible treatment alternative. This requires that the risk of recurrence, as well as the risks and side-effects associated with RT, are communicated to and discussed with the patient. It remains to be shown whether analysis of further patient and tumour characteristics can identify patient groups with lower rates of recurrence.

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