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Radiotherapy and tamoxifen after mastectomy in postmenopausal women – 20 year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II:I

Fredrika Killander[a,*], *Harald Anderson*[b], *Stefan Rydén*[c], *Torgil Möller*[b], *Knut Aspegren*[d], *Jeanette Ceberg*[b], *Christina Danewid*[b], *Per Malmström*[a]

[a]*Department of Oncology, Lund University Hospital, Lund, Sweden*
[b]*Department of Cancer Epidemiology, Lund University, Sweden*
[c]*Department of Health and Medical Service, Region Skåne, Lund, Sweden*
[d]*Faculty of Medicine, South Danish University, Odense, Denmark*

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ABSTRACT

Aims: To evaluate long-term effects of radiotherapy and tamoxifen after mastectomy on recurrence and survival in stage II breast cancer.
Methods: A randomised phase III study with three treatment alternatives. (1) Radiotherapy 50 Gy/25 fractions to chest wall and regional lymph nodes (RT). (2) Radiotherapy and tamoxifen 30 mg/day for one year (RT + tam) and 3. Tamoxifen (tam).
Results: 724 postmenopausal women were included between 1978 and 1985 and the trial was close to population based. Follow-up for survival was 23 years. Locoregional recurrences were reduced from 18.5% in the tam arm to 5.3% in the RT + tam arm. Overall mortality at 20 years was 71% in the RT arm, 68% in the RT + tam arm and 62% in the tam arm. The difference between RT + tam and tam was not significant except in the receptor positive subgroup in favour of non-irradiated patients ($p = 0.047$). The cumulative incidence of systemic disease at 20 years was lower in the RT + Tam arm than in the RT arm, 40% versus 50% ($p = 0.047$).
Conclusion: Postmastectomy radiotherapy significantly reduced loco-regional recurrences, but overall survival was not improved. At 20 years, a lower mortality was recorded for non-irradiated patients treated with tam.

1. Introduction

It is well established that postmastectomy radiotherapy very effectively decreases the risk of loco-regional recurrences.[1–6] A few studies have also demonstrated a reduced breast cancer specific mortality.[1,3,5,7] However, even though the goal of adjuvant treatment is improved breast cancer specific survival, one must take into consideration possible late side effects of treatment, and therefore also analyse overall survival. Only one randomised study of postoperative radiotherapy in postmenopausal women[4] has shown an improved overall survival and this effect has also been reported in two randomised trials in premenopausal patients.[3,5] In these three trials, the patients were also given systemic treatment and radiotherapy was standardised in contrast to previous trials.[8] Here, we report the results of a three-armed random-

* *Corresponding author:* Tel.: +46 46 177520; fax: +46 46 176080.
E-mail address: Fredrika.Killander@med.lu.se (F. Killander).
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ised trial that was initiated in 1978, when mastectomy and postoperative radiotherapy was considered the standard treatment for stage II breast cancer. The original purpose was to evaluate the effect of adjuvant medical treatment, one year of tamoxifen in postmenopausal patients, both as an addition to radiotherapy, and as an alternative. The trial was part of a breast cancer care programme in the South Swedish health care region. Early results from this trial have been reported previously,[9–12] but this is the first account on monitored data. Early, non-monitored data have also been reported to Early Breast Cancer Trialists' Collaborative Group.[1,13] From today's perspective, the primary interest concerns the long-time effects of radiotherapy and tamoxifen. According to recent guidelines postmastectomy radiotherapy is indicated if loco-regional recurrence rate exceeds 20%, which is generally the case for patients with four or more lymph node metastases.[14] For women without axillary lymph node metastases, in general, radiotherapy after mastectomy is not indicated due to a recurrence rate below 10. Treatment policy varies for women with one to three lymph nodes, and this group is therefore of special interest. When the trial started, it was claimed that the effects of tamoxifen were not entirely restricted to hormone receptor positive tumours, and thus antioestrogenic treatment was administered irrespective of hormone receptor status. With current knowledge the hormone receptor positive subgroup is of special interest.

2. Materials and methods

2.1. Patients and trial design

Postmenopausal women operated with modified radical mastectomy (MRM) at all 15 departments of surgery in South Sweden were offered inclusion in the trial. Inclusion criteria were the presence of stage II invasive mammary adenocarcinoma and age below 71 years. Postmenopausal status was defined as at least 5 years of amenorrhoea. Oestrogen and progesterone receptor measurements were not prerequisites for entering the trial. Women were randomised to three treatment alternatives: (1) post-operative radiotherapy (RT), (2) RT and tamoxifen for one year (RT + tam) and (3) tamoxifen (tam). This design makes it possible to evaluate the effect of RT in tam-treated patients by comparing the RT + tam and tam arms, and the effect of tam in irradiated patients by comparing the RT + tam arm with the RT arm. Oral informed consent was mandatory, and the trial was approved by the Research ethics committee of the faculty of Medicine, University of Lund, Sweden.

2.2. Surgery

Surgery was performed as modified radical mastectomy with en bloc dissection of level I and level II of the axilla. The major and minor pectoralis muscles were not resected, but the pectoral fascia of the major pectoralis muscles was included in the specimen. The surgical and the pathological procedures were standardised by extensive guidelines in the protocol. Microscopically radical resection of breast tumour and axillary metastases was required.

2.3. Radiotherapy

Target volume and doses were defined according to ICRU report 29.[15] A continuous target volume was defined that consisted of four parts, namely the lymph nodes of the supra- and infraclavicular fossae, the axilla, the chest wall and the ipsilateral parasternal mammary lymph nodes. The treatment techniques consisted of ventral photon beams including the supra- and infraclavicular fossae and the axilla. A smaller dorsal field with a lower weight was used for treatment of the axilla. The parasternal lymph nodes and the chest wall could be treated with either electron or photon beams based on estimates of chest wall thickness by means of tangential X-rays. The target for the parasternal mammary nodes extended from the cranial border of the second rib to the cranial border of the sterno-costal junction of the sixth rib. Specified absorbed target doses for the different volumes were 45 Gy to the fossae, 48 Gy to the axilla and parasternal nodes and 38 Gy to the chest wall. When orthovoltage X-rays were used for the chest wall, target dose was specified at a 10–15 mm depth giving a maximum skin dose of 45 Gy. All fields were treated once daily split into two series, 12 + 8 fractions, with a three week interval. Patients were treated in a supine position on a flat couch with both arms raised, and abducted about 90°. The treatment technique and dose specifications have been described in detail elsewhere.[16] The study protocol required radiotherapy to commence within four weeks after surgery.

Radiotherapy was administered at two university departments of oncology, with the exception of five cases at smaller centres using orthovoltage X-ray equipment. It has not been possible to review the radiotherapy records of these five cases.

2.4. Endocrine treatment

Oral tamoxifen (Nolvadex®, 10 mg) was given three times daily and continued for one year. The treatment was to begin within four weeks of surgery, concomitantly with radiotherapy to those patients allocated combined treatment.

2.5. Receptor status

Hormone receptor measurements were performed on all properly frozen tumour samples at the research laboratory of the Department of Oncology, Lund University Hospital, as has been described elsewhere.[9] Cut-off points of 10 fmol specifically bound 3H-oestradiol/mg protein (ER) and 30 fmol specifically bound 3H-R 5020/mg protein (PgR) were chosen to define ER and PgR-positivity. We have chosen to classify a tumour as receptor positive if either ER and/or PgR were positive.

2.6. Follow-up and ascertaining data from patient records

Clinical examinations were performed every three months the first three years, every four months the fourth year, twice yearly the fifth year and then once yearly. Chest X-rays, bone scintigraphy and biochemical tests were performed twice yearly the first two years, and then once every year. Mammography of the contra lateral breast was performed once every year. The protocol stated follow-up for 6 years, but most

patients were followed with clinical examinations for a considerably longer time. During 2003, we did a complete review of the patient records with the aim to follow-up all the women for breast and other events until 31st December, 2002. All 15 participating hospitals were visited, and patient records were also requested from other hospitals if patients had moved. Since complete follow-up of women that moved from the catchment region of the randomising clinic was not obtained it was decided to censor follow-up for breast events when a woman moved from the community in which she lived at inclusion. The latter information was obtained from the National Population register.

Information about treatment compliance, side effects of radiotherapy such as arm oedema, brachial plexopathy and pneumonitis requiring treatment was collected retrospectively. In one institution, more than 80% of the randomised patients' records were destroyed. Since the missing records very well might differ systematically from those retained, all patients from this institution were excluded (6% of all randomised patients), except in analyses of overall survival.

Information about other malignant diseases was supplemented with data from the National Cancer Registry, and information about cause of death was supplemented with data from the National Cause of Death Register. Dates of death and emigration were obtained from the National Population Register until 30 September, 2004, and thus all the women were followed for survival until this date.

2.7. *Endpoints, randomisation and statistical methods*

According to the protocol from 1978 the study endpoints were time to recurrence, type of recurrence and overall survival. In the present long-term analysis, we have added time to systemic disease, incidence of other events and side effects. A local recurrence was defined as the appearance of tumour in the skin, subcutaneous tissues or muscles of the chest wall. A regional recurrence was defined as metastasis to the lymph nodes of one or more of the following nodal groups; axillary apex, supraclavicular fossa and the parasternal lymph nodes. We considered loco-regional recurrences only as first event of recurrence or synchronous with distant metastases (four patients). Thus, in the analyses of loco-regional recurrences, death and distant recurrence were competing events.

Time to systemic disease was defined as time to the first of the events distant metastases or death from breast cancer. In the analyses of time to systemic disease, non-breast cancer death in a woman without distant metastases was a competing event.

The randomisation was stratified on department, tumour size and number of positive axillary nodes (*N*0, *N*1–3, and $N \geqslant 4$) with block size six within strata, and it was performed by calling a central secretariat in which a closed envelope with a prerandomised allocation was selected. The identity of the patient, date, department and allocated treatment was documented by the secretariat. The allocated treatment was also reported, by each institution, on case report forms to the data centre. By mistake the secretariat did not record the allocated treatment for the first 47 patients, but only date, their identity and institution. Since the correspondence between the allocated treatment as recorded by the secretariat and reported by the respective institutions for the rest of the patients is very good (98%), we have chosen to keep the first patients in the study, and for these use the randomised treatment as reported by the respective departments. This explains the small discrepancy in the number of patients compared to earlier publications of this study.[1,10,12,13] All endpoints were analyzed according to the intention to treat principle. Survival and other time to event end-points were determined from date of randomisation and analysed by survival analysis techniques. Times to loco-regional recurrence and systemic disease are illustrated by means of cumulative incidence curves, considering the competing risks of other events. The cumulative incidence of, e.g. systemic disease at 10 years is the probability to develop metastases before 10 years and before death without metastases.[17,18] Time to death is illustrated by means of cumulative mortality curves. The log (–log) transform and normal approximation[19] was used to determine confidence intervals for cumulative incidence and mortality and to compare treatment arms at the fixed times 10 and 20 years. We have chosen to censor follow-up for recurrences when a woman moved from the community in which she lived at inclusion in the study. This might bias the results if women that move are more (or less) prone to recur than women who do not move. To study if moving affected overall mortality, time of moving was used as a time dependent covariate in a Cox proportional hazard model.

3. Results

3.1. *Patient characteristics and follow-up*

Seven hundred and twenty four patients were randomised from 1978 to 1985 (Fig. 1). Eleven patients were excluded due to major violation of entry criteria; two had not undergone modified radical mastectomy and nine had evidence of disseminated disease at randomisation. Hence 713 patients could be followed up for survival, and 668 were fully evaluable (Table 1).

At study entry, median age was 63 years. Median tumour size was 25 mm and the median number of examined lymph nodes was 10 (p10–p90: 5–17 lymph nodes). Oestrogen and/or progesterone receptor status was analysed in 444 of 668 patients; in 374 cases for both receptors, in 69 cases only for ER, and in one case only for PgR. The proportion of the 444 patients with either positive ER or PgR was 70%. The relation left: right sided tumours was 52%:48%. Characteristics of the patients were reasonably well balanced and are presented in Table 1. The 45 patients from the hospital where patient charts were missing, were evenly distributed in the different treatment groups, and are not included in Table 1. A few patients in each treatment group (3–5%) that were amenorrhoic but did not fulfill the entry criteria of at least five years since cessation of menses, were not excluded from the analysis. A flow-chart of the trial according to Consort is shown in Fig. 1.[20] In 8% (48/668) follow-up for recurrence was censored when a women moved from the community in which she lived at randomisation. The fact that a woman moved did not significantly affect her future mortality compared to non-movers (HR = 0.88, 95% CI 0.58–1.33). Median age at diagnosis was quite similar, also supporting that censoring

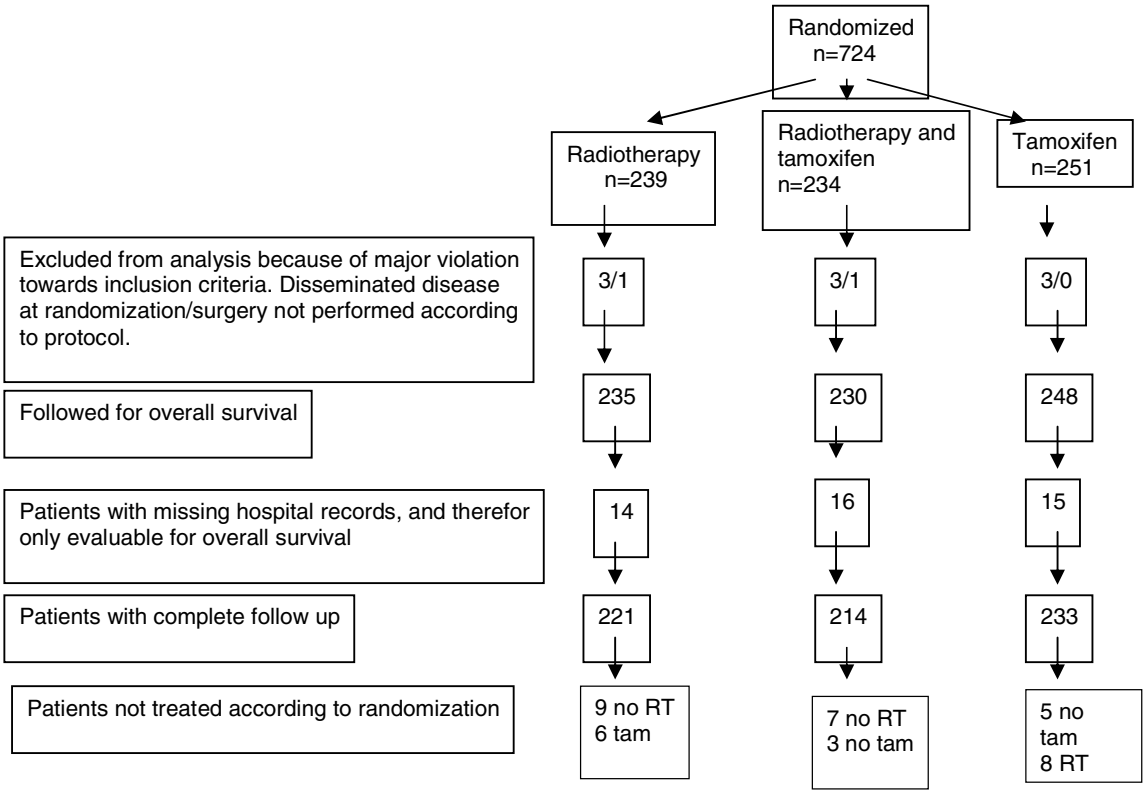

Fig. 1 – Flow diagram for the SBII:I trial.

Table 1 – Characteristics of 668 fully evaluable patients in the three different treatment arms in the SBII:I trial

	RT, $n = 221$	RT + Tam, $n = 214$	Tam, $n = 233$
Median age (years)	63	63	62
Premenopausal patients (number)	9	7	13
Median tumour size (mm)	25	22	25
Number of positive lymph nodes (%)			
pN0	90 (41%)	85 (40%)	96 (41%)
pN1–3	91 (41%)	79 (37%)	94 (40%)
pN $\geqslant$ 4	36 (16%)	44 (21%)	40 (17%)
Number of positive nodes not known			
N+	4 (2%)	6 (3%)	3 (1%)
Hormone receptor status (number of patients with)			
ER+ and/or PgR+	101	110	102
ER− and PgR−	40	34	57
Rec unknown	80	70	74

was uninformative. For systemic disease median follow-up was 20.3 years for 202/668 (30%) patients alive without metastases at the end of follow-up. For overall survival 176/713 patients (24.7%) were still alive at the end of follow-up (30 September, 2004), and their median follow-up was 22.9 years.

3.2. *Treatment*

Median time from surgery to start of radiotherapy was 42 days, and median time from surgery to start of tamoxifen treatment was 20 days. Median treatment time with tamoxifen was 12 months (range 1–72). Among fully evaluable patients, 3.7% of those allocated to radiotherapy did not receive it, and similarly 1.8% of the patients who were allocated to tamoxifen did not receive this treatment. On the other hand, 2.7% and 3.4% of women got, respectively, Tam and RT without being randomised to these treatments (Fig. 1).

3.3. *Loco-regional recurrences*

The cumulative incidence of loco-regional recurrences as first event at 20 years of follow-up was significantly reduced, with 71%, by radiotherapy ($p < 0.001$), 18.5% (95% CI 13.8–23.8%) in

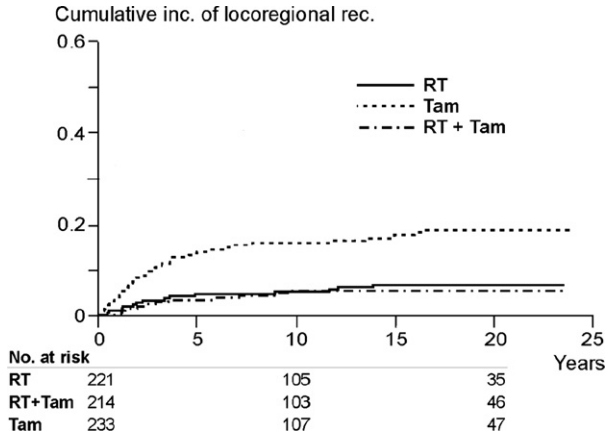

Fig. 2 – Cumulative incidence of loco-regional recurrences as first event by treatment arm in 668 fully evaluable patients.

Table 2 – Cumulative incidence (95% confidence interval), at 20 years, of loco regional recurrences in 668 patients as first event, or synchronically with distant metastases, in relation to axillary lymph node metastases at primary surgery, and in different treatment groups

	RT, $n = 221$	RT + Tam, $n = 214$	Tam, $n = 233$
N0	3.5% (0.9–9.0%)	5.9% (2.2–12.3%)	6.7% (2.7–13.2%)
N1–3	8.1% (3.6–15.1%)	2.6% (0.5–8.3%)	25.9% (17.5–35.1%)
N4–	11.4% (3.6–24.1%)	9.4% (3.0–20.4%)	25.5% (13.3–39.7%)
All patients	6.7% (3.8–10.4%)	5.3% (2.8–8.9%)	18.5% (13.8–23.8%)

the tam-only arm, versus 5.3% (95% CI 2.8–8.9%) and 6.7% (95% CI 3.8–10.4%) in patients randomised to RT with and without tamoxifen (Fig. 2). In all, there were 67 loco-regional recurrences; four of these were synchronous with distant metastases. In the non-irradiated patients (42 loco-regional recurrences), the failure sites were the mastectomy scar and chest wall ($n = 25$, 59%), the axilla ($n = 10$, 24%), supra clavicular fossa ($n = 2$%, 5%) and different combinations ($n = 5$%, 12%, where the axilla was represented in two cases). In the irradiated patients (25 loco-regional recurrences), the failure sites were the mastectomy scar and chest wall ($n = 16$%, 64%), the axilla ($n = 1$%, 4%), the supra clavicular fossa ($n = 4$%, 16%) and different combinations ($n = 4$%, 16% where the axilla was represented in two cases). No isolated recurrences were reported in ipsilateral parasternal lymph nodes or in the inferior clavicular fossa.

Loco-regional recurrences in relation to axillary lymph node status are shown in Table 2. It is notable that in N0 patients, only 7% loco-regional recurrences were diagnosed after 20 years in the Tam group, versus 6% in the RT + Tam group. In the N1–3 subgroup, the incidence was 25.9% (95% CI 17.5–35.1%) in the Tam arm, and 2.6% (95% CI 0.5–8.3%) in the RT + Tam arm. Among patients who developed loco-regional recurrences, the majority later developed distant metastases in spite of salvage therapy. Salvage treatment after recurrence was thus successful in 31% (13/42) of patients non-irradiated after mastectomy but only in 4% (1/25) of irradiated patients.

3.4. *Cumulative incidence of systemic disease*

At 20 years the cumulative incidence of systemic disease was 50% in the RT group, 40% in the combination arm and 45% in the tamoxifen arm (Fig. 3a $p = 0.33$ comparing RT + Tam versus Tam, and $p = 0.047$ comparing RT vs RT + Tam) (Table 3a). Considering only receptor positive patients the numbers were 54%, 40% and 41%, respectively ($p = 0.047$ comparing RT versus RT + Tam, Fig. 3b). Among patients with 1–3 involved lymph nodes the incidences were 58% in the RT arm, 36% in the combination arm, and 51% Tam arm ($p = 0.007$ comparing RT versus RT + Tam and $p = 0.047$ comparing RT + Tam versus Tam, Fig. 3c). In patients with more than three lymph nodes, there was a significant difference between RT and RT + Tam 88% versus 67% ($p = 0.02$). No significant differences were recorded for node negative patients.

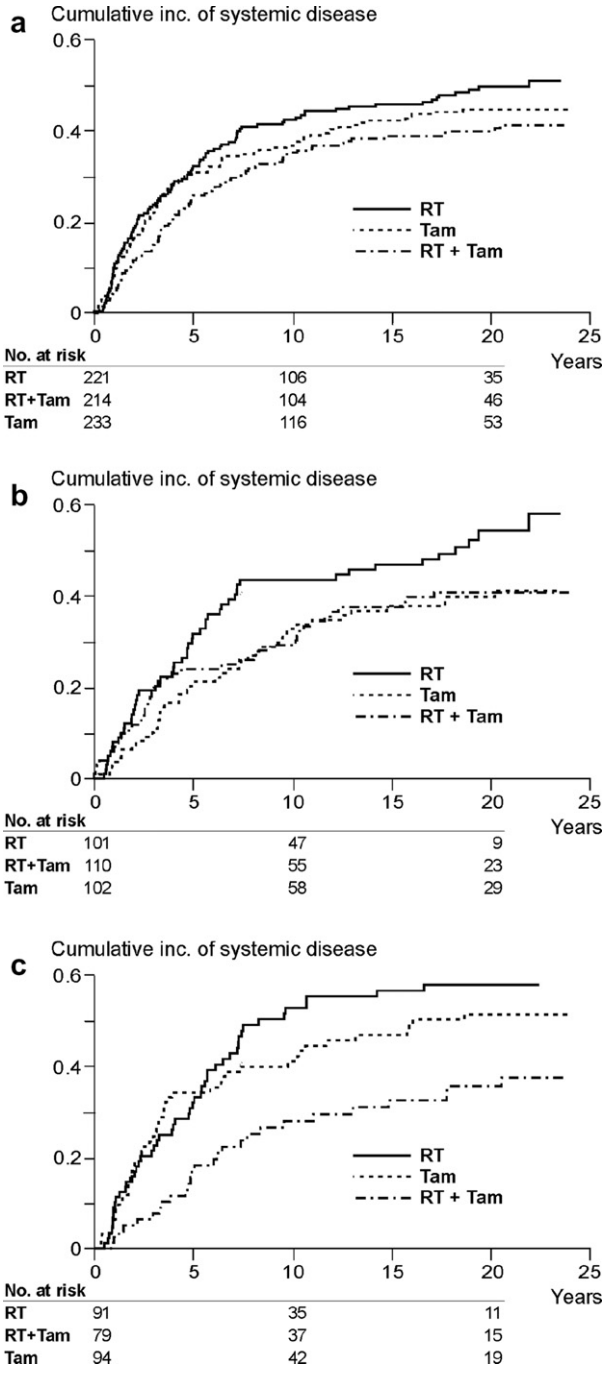

Fig. 3 – Cumulative incidence of systemic disease by treatment arm in: (a) 668 fully evaluable patients, (b) receptor positive patients ($n = 313$) and (c) patients with 1–3 positive axillary lymph nodes at primary surgery ($n = 264$).

3.5. *Overall mortality*

Overall mortality for the 713 randomised patients, at 20 years was 71% in the RT arm, 68% in the RT + Tam arm, and 62% in the Tam arm (Fig. 4a, Table 3b). The difference between RT + Tam versus Tam was not significant ($p = 0.14$). Nor was there any significant difference between RT and RT + Tam ($p = 0.50$). Considering hormone receptor positive patients the mortality rates at 20 years were 74% in the RT arm, 67%

Table 3a – Cumulative incidence of systemic disease at 10 and 20 years by treatment arm in 668 fully evaluable patients, and in subgroups by receptor and axillary lymph node status

		RT	RT + Tam	Tam
Cumulative incidence of systemic disease (%) (95% confidence interval)				
All patients, *n* = 668	10 years	42 (36–49)	35 (29–42)	37 (30–43)
	20 years	50 (43–56) 0.047[a]	40 (33–46)	45 (38–51)
Receptor positive, *n* = 313	10 years	44 (33–53)	33 (24–42)	29 (20–38)
	20 years	54 (43–64) 0.047[a]	40 (30–49)	41 (31–50)
Receptor negative, *n* = 131	10 years	43 (28–58)	54 (36–69)	56 (42–68)
	20 years	43 (28–58)	54 (36–69)	62 (48–74)
N0, *n* = 271	10 years	21 (14–30)	26 (17–36)	19 (12–28)
	20 years	27 (18–37)	30 (20–40)	25 (17–34)
N1–3, *n* = 264	10 years	53 (42–63) 0.002[a]	28 (18–38)	41 (31–51)
	20 years	58 (46–68) 0.007[a]	36 (25–46) 0.047[b]	51 (41–61)
N4+, *n* = 120	10 years	67 (50–79)	67 (50–79)	69 (52–81)
	20 years	88 (72–96) 0.021[a]	67 (50–79)	74 (57–85)

a *p*-values comparing RT versus RT + Tam, non-significant values not shown.
b *p*-values comparing RT + Tam versus Tam, non-significant values not shown.

Table 3b – Overall mortality at 10 and 20 years by treatment arm in all randomised 713 patients, in 668 fully evaluable patients, and in subgroups by receptor and axillary and lymph node status

		RT	RT + Tam	Tam
Overall mortality (%) (95% confidence interval)				
All patients, *n* = 713	10 years	43 (37–49)	42 (36–49)	43 (37–50)
	20 years	71 (65–77)	68 (62–74)	62 (56–68)
All evaluable patients, *n* = 668	10 years	43 (37–50)	41 (35–48)	45 (39–51)
	20 years	71 (65–77)	67 (61–73)	63 (57–69)
Receptor positive, *n* = 313	10 years	44 (35–54)	39 (31–49)	37 (29–47)
	20 years	74 (65–82)	67 (59–76) 0.047[a]	54 (45–64)
Receptor negative, *n* = 131	10 years	50 (36–66)	47 (32–65)	60 (47–72)
	20 years	70 (56–83)	62 (46–78)	74 (62–84)
N0, *n* = 271	10 years	30 (22–41)	29 (21–40)	28 (20–38)
	20 years	61 (51–71)	58 (48–68)	53 (44–63)
N1–3, *n* = 264	10 years	45 (36–56)	39 (30–51)	50 (40–60)
	20 years	74 (65–83)	65 (55–76)	64 (54–73)
N4+, *n* = 120	10 years	72 (57–86)	64 (50–77)	72 (58–85)
	20 years	92 (80–98)	84 (72–93)	85 (72–94)

a *p*-values comparing RT + Tam versus Tam, non-significant values not shown.

in the combination arm, and 54% in the Tam group. No statistically significant difference was seen when comparing RT to RT + Tam ($p = 0.28$) but the comparison of RT + Tam versus Tam was significant in favour of patients not receiving radiotherapy ($p = 0.047$, Fig. 4b). In the N1–3 group, mortality at 20 years was 74%, 65% and 64% (ns) Fig. 4c.

3.6. *Contralateral breast cancer, other cancers and side effects of radiation*

No difference was seen in the number of contra-lateral breast cancer in the different arms; the frequency varied between 4% and 6%. Nor was there any difference in reported cases of endometrial cancer, or any other cancer types. 6.8% (73/435) of irradiated patients developed lymphoedema as opposed to 3.9% (9/233) in only operated patients. Radiation pneumonitis requiring treatment was infrequent, 3.9%, in irradiated patients and brachial plexopathy was found in two irradiated patients (0.5%).

4. Discussion

This trial belongs to the early generation of radiotherapy trials, in which radiation was combined with systemic adjuvant treatment after modified radical mastectomy. The study has some strong qualities worth mentioning; it is close to popula-

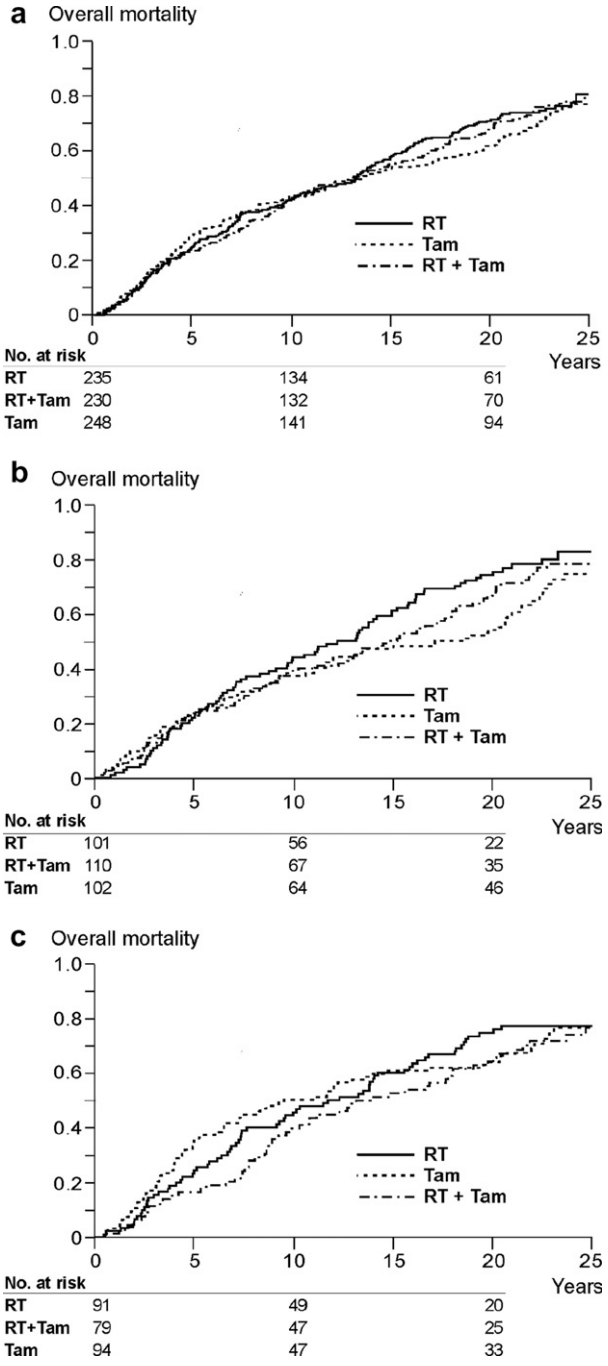

Fig. 4 – Overall mortality in: (a) all 713 randomised patients, (b) receptor positive patients (*n* = 313) and (c) patients with 1–3 positive axillary lymph nodes at primary surgery (*n* = 264).

tion based, the coverage was 81% of all eligible patients,[11] no patients were lost to follow-up regarding vital status as all patients could be followed in the national population register, and the median follow-up time of those alive was 23 years. Follow-up was incomplete for breast events in those who moved, but this probably did not result in any bias since there was no significant effect on mortality. Unfortunately, one center's patients had to be excluded from all analyses except for survival because of the fact that most patient charts had been destroyed. This center represented only 6% of the randomised patients, though. There is an imbalance in the number of patients in the different treatment groups (*n* = 239, 234 and 251) (Fig. 1), but this is reasonable considering the large number of strata and the randomisation procedure ($\chi^2 = 0.63$, 2 df, $p > 0.5$ when testing for full randomisation).

A very clear relative reduction in loco-regional recurrences, 71%, was obtained with radiotherapy in common with the vast majority of adjuvant radiotherapy trials.[5,3,4,21,22,2,6,1] This effect was most pronounced in the *N*1–3 group, with a risk reduction of 90%, as also demonstrated in a Danish study,[4] and in a retrospective analysis of three EORTC trials.[23] No radiotherapy effect was discernible in the rather large group of stage II patients with no lymph node metastases. In this group the frequency of loco-regional recurrences already is low without radiotherapy, and the number needed to treat to avoid one recurrence is high as has also been demonstrated in several other studies.[22–24]

In our study, the most common loco-regional failure site after the mastectomy scar and chest wall among non-irradiated patients was the axilla, and not as in some other studies[25–27] the supraclavicular fossa. This may suggest that axillary surgery was less extensive than in other trials even if the median number of removed nodes was 10. However, radiotherapy was as effective in reducing recurrence in the axilla as on the chest wall. The fact that salvage treatment of local recurrences fail in the majority of non-irradiated patients, 2/3 in this trial, underlines the importance of identifying prognostic factors for selection of patients with a high risk for local recurrence to enable immediate postoperative radiotherapy.

Radiotherapy as an addition to tam treatment did not significantly lower the cumulative incidence of systemic disease at 20 years considering all patients. In one subgroup, the *N*1–3 patients, an improvement was found ($p = 0.047$) (Table 3a), but this result has to be interpreted with caution. At 20 years of follow-up, one year of tamoxifen treatment significantly lowered the cumulative incidence of systemic disease in all patients and also in the subgroups *N*1–3 and receptor positive patients. The reduction observed in the receptor positive patients is similar to that presented in the meta-analysis of EBCTCG 05.[13]

The addition of external radiotherapy to tamoxifen did not improve survival after 20 years. This is in sharp contrast to the very similar Danish trial, DBCG82c[4] in which a survival advantage of 10% at 10 years for the combination was reported, but where 20 year overall survival data has not yet been published. Patients included in the trials were, however, different. A significantly smaller proportion in the Danish study was *N*0 patients, 10% versus 40% in SBII:I, and furthermore, they were selected for high risk of recurrence. Only T2 tumours were included in the Swedish trial as opposed to the Danish trial which also included both T3 and T4 tumours. However, when comparing the *N*+ patient groups in these two trials, at 10 years of follow-up, a very similar pattern is seen. When adding RT to tam the absolute reduction in overall mortality for patients with 1–3 positive nodes was 11% in both trials (39% versus 50% in SBII:I and 45% versus 56% in DBCG 82 c). For patients with more than three nodes the reductions were 8% and 7%, respectively (64% versus 72% in SBII:I and 76% versus 83% in DBCG 82 c).

The effect of radiotherapy did not seem to be consistent over follow-up time. During the first 5–10 years RT + tam fared better than tam (Fig. 4a and c) but during the period 10–20 years, the benefit of the combination was lost as the survival curves merged and finally crossed over, suggesting late radiotherapy-related mortality, as has been shown in other trials with long follow-up. In one subgroup analysis, for receptor positive patients, overall mortality was significantly lower for patients treated with tam only compared to RT + tam (54% versus 67% $p = 0.047$) also suggesting late toxicity of RT (Table 3b and Fig. 4b).[1,28–30] The interesting publication of Höjris et al.[31] did not demonstrate any significant late non-breast cancer mortality in the Danish trials,[3,4] claiming that the radiotherapy technique used in these trials was safe. However, the median follow-up was 9.75 years and presumably too short to allow for the full impact of late side effects of radiotherapy. Longer follow-up of the Danish post-menopausal trial, concerning overall survival, will be of great interest.

In summary, the SBII:I trial showed a significant reduction of loco-regional recurrences with postmastectomy radiotherapy in patients with lymph node metastases. The large subgroup of N0 patients did, however, not benefit from RT. No improvement after radiotherapy in overall survival was seen at 20 years. However, results closely similar to the Danish trial DBCG 82C was seen after 10 years for the subgroup of patients with lymph node metastases indicating early beneficial effects of combined treatment that was lost with a longer follow-up. With modern radiotherapy techniques, late side effects are likely to be fewer. In our view the result of the present trial strengthens the case for postmastectomy radiotherapy for breast cancer patients with 1–3 lymph node metastases. Further study of radiotherapy after mastectomy is still warranted as is being undertaken in the SUPREMO trial, organised by the Medical Research Council in United Kingdom (MRC) and EORTC. Furthermore, better prognostic factors for loco-regional recurrences in both N0 and N+ patients, as well as predictive factors for resistance to radiotherapy, are needed for future individualisation of treatment.

Conflicts of interest statement

None declared.

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