Original article

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# Adjuvant therapy after excision and radiation of isolated postmastectomy locoregional breast cancer recurrence: definitive results of a phase III randomized trial (SAKK 23/82) comparing tamoxifen with observation

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**Background:** Adjuvant systemic treatment for patients with isolated locoregional recurrence (ILRR) of breast cancer is based on a single reported randomized trial. The trial, conducted by the Swiss Group for Clinical Cancer Research, compared tamoxifen (TAM) with observation after complete excision of the ILRR and proper radiotherapy. We performed a definitive analysis of treatment outcome at >11 years of follow-up, after the majority of the patients had a subsequent event of interest.

**Patient and methods:** One hundred and sixty-seven patients with 'good-risk' characteristics of disease were randomized. 'Good-risk' was defined as estrogen receptor expression in the ILRR, or having a disease-free interval of >12 months and a recurrence consisting of three or less tumor nodules, each ≤3 cm in diameter. Seventy-nine percent of the patients were postmenopausal at randomization.

**Results:** The median follow-up time of the surviving patients was 11.6 years. The median post ILRR disease-free survival (DFS) was 6.5 years with TAM and 2.7 years with observation ($P = 0.053$). The difference was mainly due to reduction of further local relapses ($P = 0.011$). In postmenopausal patients, TAM led to an increase of DFS from 33% to 61% ($P = 0.006$). In premenopausal women, 5-year DFS was 60%, independent of TAM medication. For the whole study population, the median post-recurrence overall survival (OS) was 11.2 and 11.5 years in the observation and the TAM group, respectively; premenopausal patients experienced a 5-year OS of 90% for observation compared with 67% for TAM ($P = 0.175$), while the respective figures for post-menopausal patients were both 75%.

**Conclusions:** These definitive results confirmed that TAM significantly improves the post-recurrence DFS of patients after local treatment for ILRR. This beneficial effect does not translate into a detectable OS advantage.

**Key words:** breast cancer, locoregional recurrence, randomized phase III study, tamoxifen

## Introduction

Isolated locoregional recurrence (ILRR) after mastectomy has been associated with a worse prognosis than breast recurrence after breast-conserving surgery for primary breast cancer. Despite aggressive local treatment, almost all patients with ILRR after mastectomy are believed to develop distant metastases eventually [1]. Progression-free survival at 7 years was 30% in a recent series of 337 patients who developed ILRR as first relapse manifestation. Eighty percent of these patients had undergone a mastectomy and 20% a lumpectomy and breast radiation for their primary breast cancer [2]. In a more mature series from the Joint Center for Radiation Therapy, the actuarial rate of freedom from distant metastases was only 7% at 10 years [3].

The role of systemic adjuvant treatment is well established in the management of primary breast cancer, but only one randomized phase III study has been performed to examine tamoxifen (TAM) for ILRR. In a first analysis of this trial, conducted from 1982 to 1991, we have demonstrated that TAM significantly prolongs post-ILRR disease-free survival (DFS) at a median observation time of 6.4 years. There was a more pronounced effect on the reduction of further local relapses than on the reduction of distant metastases. Patients eligible for this study had rather favorable disease characteristics, such as positive estrogen-receptors or, in the case of unknown receptor status, not more than three nodules, each ≤3 cm in diameter, and a disease-free interval (DFI) from primary treatment of at least 1 year [4]. A subsequent analysis indicated that TAM was associated with increased distant failure

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rates in premenopausal patients, while both distant and local progression rates were reduced in postmenopausal patients [5]. TAM had no significant impact on overall survival (OS). However, the median survival duration of the study population had not been reached at a median follow-up of 6.4 years. This is the only randomized study available on systemic therapy of ILRR to reach its accrual goal. Since even the retrospective series on this subject are generally small in size, it was important to analyze the mature long-term follow-up data of this randomized study. We present here the results of these analyses at a median follow-up of 11.6 years for surviving patients.

## Patients and methods

The study design was described previously [4]. One hundred and sixty-seven 'good risk' women with ILRR—defined as first reappearance of cancer in the ipsilateral (side of the primary tumor) chest wall, shoulder, neck and upper arm, or the axillary, infraclavicular, supraclavicular and cervical lymph nodes on either side—were included in the study. 'Good risk' was defined as estrogen receptor (ER) positivity of the recurrence or, in the case of unknown ER receptor status, a DFI of >12 months, and less than four recurrence nodules with a maximal diameter of 3 cm. Premenopausal status was defined as occurrence of the last menstruation within 1 year from study entry or, in case of a previous hysterectomy, patient age of <52 years. ER/progesterone receptor levels of ≥10 fmol/mg cytosol protein using standard methods were considered positive. Patients pretreated with adjuvant tamoxifen were not eligible for this study.

The local treatment consisted of radical excision followed by local radiotherapy of the recurrence site. A total dose of 5000 cGy was given to the involved region at 200 cGy per fraction, 5 days a week. Patients were stratified according to menopausal status, adjuvant chemotherapy and axillary node involvement at diagnosis, and centrally [Swiss Group for Clinical Cancer Research (SAKK) Coordinating Center, Bern] randomized by telephone to either observation or systemic treatment (tamoxifen 20 mg per day orally) until disease progression.

The Kaplan–Meier method was used to estimate distributions of DFS and OS [6]. Differences in survival distributions were evaluated using the log-rank test [7] and, additionally, for the DFS using the Gehan–Wilcoxon test. The difference between the two tests is that the Gehan–Wilcoxon test places more weight on the beginning of the survival curve and less on the end, whereas the log-rank test places equal weight upon both. A multivariate analysis using the Cox proportional hazards model was performed (SAS v. 8.2, SAS Institute Inc., Carey, NC; S-PLUS v. 6, Insightful Corp., Seattle, WA) [8]. The interaction between treatment and menopausal status was tested as described previously [9]. Cumulative incidence functions totalling the overall event probability were estimated for the competing events and compared between the treatment arms [10, 11]. All *P* values were derived from a two-sided test for significance.

## Results

### Patient characteristics

One hundred and seventy-eight patients entered this study and were randomized to TAM or observation after resection and radiotherapy for ILRR of breast cancer. Eleven of 178 patients were ineligible (6%) due to reasons detailed in the initial publication of this study [4]. Disease and patient characteristics are summarized in Table 1. The median follow-up time for this study was 11.6 years for surviving patients.

**Table 1.** Characteristics of surviving patients

| Characteristics | Observation (*n* = 40) | | TAM (*n* = 39) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Age (years) | | | | |
| Median | 52 | | 57 | |
| Range | 35–75 | | 35–70 | |
| Disease-free interval (months) | | | | |
| Median | 45 | | 39 | |
| Range | 2–175 | | 3–149 | |
| Primary tumor size (cm) | | | | |
| <2 | 16 | 40 | 12 | 31 |
| 2–5 | 23 | 58 | 25 | 64 |
| >5 | 1 | 3 | 1 | 3 |
| Unknown | 0 | 0 | 1 | 3 |
| Axillary node involvement | | | | |
| Negative | 25 | 63 | 21 | 54 |
| Positive | 15 | 38 | 15 | 38 |
| Unknown | 0 | 0 | 3 | 8 |
| Adjuvant chemotherapy | | | | |
| Yes | 18 | 45 | 15 | 38 |
| No | 22 | 55 | 23 | 59 |
| Unknown | 0 | 0 | 1 | 3 |
| Locoregional recurrence | | | | |
| Localization | | | | |
| Skin ± chestwall | 38 | 95 | 34 | 87 |
| Lymph nodes ± skin | 2 | 5 | 5 | 13 |
| Hormonal receptors (ER and PgR) | | | | |
| Determined | 25 | 63 | 26 | 67 |
| Not determined | 15 | 38 | 13 | 33 |
| Menopausal status | | | | |
| Premenopausal | | | | |
| Nodal status at diagnosis of primary | | | | |
| Negative | 9 | 64 | 3 | 43 |
| Positive | 5 | 36 | 3 | 43 |
| Unknown | 0 | 0 | 1 | 14 |
| Estrogen receptor status | | | | |
| Positive | 8 | 57 | 4 | 57 |
| Unknown | 6 | 43 | 3 | 43 |
| Previous adjuvant chemotherapy | | | | |
| Yes | 6 | 43 | 3 | 43 |
| No | 8 | 57 | 3 | 43 |
| Unknown | 0 | 0 | 1 | 14 |
| Postmenopausal | | | | |
| Nodal status at diagnosis of primary | | | | |
| Negative | 16 | 62 | 18 | 56 |
| Postitive | 10 | 38 | 12 | 38 |
| Unknown | 0 | 0 | 2 | 6 |
| Estrogen receptor status | | | | |
| Positive | 17 | 65 | 22 | 69 |
| Unknown | 9 | 35 | 10 | 31 |
| Previous adjuvant chemotherapy | | | | |
| Yes | 12 | 46 | 12 | 38 |
| No | 14 | 54 | 20 | 63 |

ER, estrogen receptor; PgR, progesterone receptor; TAM, tamoxifen.

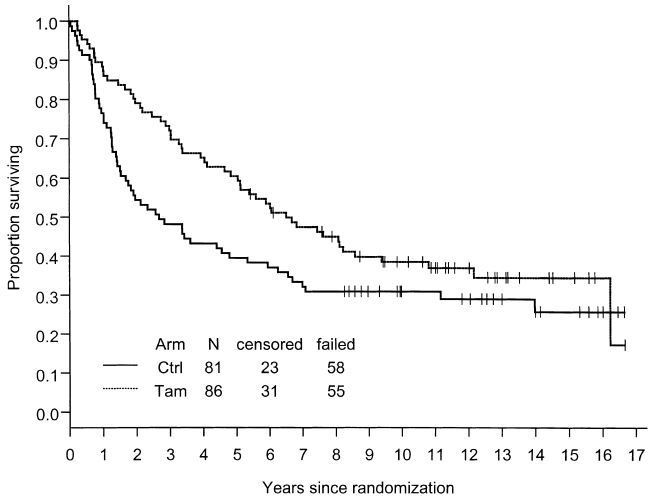


**Figure 1.** Disease-free survival by treatment. Ctrl, control; Tam, tamoxifen.

### Disease-free survival

Disease-free survival was calculated from the day of randomization until the first event. Possible events were breast cancer recurrence (local, distant or both), second malignancy or death. The median time to first event was 2.7 years with observation alone and 6.5 years in the TAM arm (log-rank $P = 0.053$) (Figure 1). This difference was even more significant if it was assumed that the occurrence of relapses was not evenly distributed over time (Gehan–Wilcoxon $P = 0.008$). The 5-year DFS rates were 61% in the TAM arm and 40% in the observation arm. There were four new events in the TAM arm and two new events in the observation arm after 9 years. Table 2 lists the results of the multivariate analysis to examine the influence of a variety of factors on DFS. Treatment with TAM and a DFI >12 months from first treatment of breast cancer to local relapse were prognostic for a longer DFS. Menopausal status also became a significant prognostic factor for DFS, since postmenopausal patients were at greater risk for relapse ($P = 0.051$). Nodal involvement at study entry was of borderline significance ($P = 0.071$).

Table 3 lists the results of the cumulative incidence analysis of the different types of further relapse at 3, 5 and 10 years. In accordance with the first analysis of this study, only further local recurrences were significantly reduced by TAM treatment. The cumulative incidence of local and distant failure is shown in Figure 2A and B. Other events, such as death or second cancer, were too rare to allow statistical analysis.

### Overall survival

Overall survival was calculated from the day of randomization until the date of death or the date the patient was last known to be alive. Median survival times were 11.5 and 11.2 years in the TAM and observation arms, respectively ($P = 0.79$) (Figure 3). The 5-year survival rate was 73% in the TAM arm and 79% in the observation arm. Of the 167 patients, 40 are still alive with observation alone and 39 are undergoing treatment with TAM. Table 4 lists the results of the multivariate analysis to examine the influence of a variety of factors on OS. DFI >12 months from first treatment of breast cancer to local relapse, patient age (cut-off point arbitrarily set at 65 years) and nodel involvement at study entry had a significant impact on OS.

### Menopausal status and outcome

The Kaplan–Meier distribution of DFS for both menopausal and treatment groups is shown in Figure 4. TAM had a significant impact on relapse reduction only in postmenopausal patients. In premenopausal women, 5-year DFS was 60% both with and without TAM. The corresponding figures were 61% and 33%, respectively, in the postmenopausal patient group ($P = 0.006$).

The Kaplan–Meier distribution of OS for both menopausal and treatment groups is plotted in Figure 5. Premenopausal control patients seem to have a better survival compared with the other groups, although this difference did not reach statistical significance. The 5-year survival for premenopausal control patients was exceptionally good (90%), while premenopausal TAM patients had a 5-year OS of only 67% ($P = 0.175$). These observations should be interpreted with caution, since the group of premenopausal patients is small ($n = 35$). The 5-year OS of both postmenopausal patient arms was 75%. There were no events such as death due to pulmonary embolism or endometrial cancer in both menopausal groups, which could have been attributed to the effect of TAM.

## Discussion

These are the mature results of the randomized SAKK study addressing the question of systemic treatment for ILRR after mastectomy. In the first analysis at 6.3 years median follow-up, 5-year DFS was significantly improved with TAM, from 36% to 59% [4]. In the present long-term analysis at a median follow-up of 11.6 years for surviving patients, we can show that the positive impact of TAM on DFS is real and persistent. The current analysis demonstrates a 5-year DFS of 40% in the observation group and 61% in the TAM group.

The positive impact of TAM on DFS did not translate into a survival benefit. Different factors might have been responsible for this fact, such as small patient numbers and the low number of events. The analyses by menopausal status showed that the beneficial effect of TAM on DFS was confined to postmenopausal patients. This group is also most at risk for death events unrelated to breast cancer, and the positive impact of TAM on DSF might thus not have enough time to influence OS in this age group. Premenopausal patients did not benefit from TAM in terms of DFS. Rather unexpectedly, premenopausal women seemed to be at greater risk of death if treated with TAM compared with observation. These differences, however, were not statistically significant and the patient numbers in the respective subgroups were small. TAM-induced toxicity would be an explanation for this unexpected finding; however, there was no evidence for TAM-associated life-threatening complications or secondary cancers in our patients. Since most deaths occurred due to disease progression, we speculate that

**Table 2.** Multivariate analysis of disease-free survival

| Variable | Hazard ratio | 95% confidence interval | *P* value |
|---|---|---|---|
| Treatment | | | |
| Surgery + radiotherapy | 1.00[a] | | |
| Surgery + radiotherapy + tamoxifen | 0.57 | 0.39–0.84 | 0.004 |
| Disease-free interval | | | |
| ≤12 months | 1.00[a] | | |
| >12 months | 0.48 | 0.26–0.88 | 0.017 |
| Primary tumor size | | | |
| <2 cm | 1.00[a] | | |
| ≥2 cm | 1.25 | 0.81–1.92 | 0.325 |
| Pretreatment adjuvant chemotherapy | | | |
| Yes | 1.00[a] | | |
| No | 1.44 | 0.81–2.56 | 0.210 |
| Nodal involvement (primary tumor) | | | |
| Negative | 1.00[a] | | |
| Positive | 1.55 | 0.88–2.71 | 0.128 |
| Menopausal status (first relapse) | | | |
| Premenopausal | 1.00[a] | | |
| Postmenopausal | 1.71 | 1.00–2.92 | 0.051 |
| Skin lesion (first relapse) | | | |
| No | 1.00[a] | | |
| Yes | 1.04 | 0.57–1.90 | 0.889 |
| Nodal involvement (first relapse) | | | |
| No | 1.00[a] | | |
| Yes | 1.79 | 0.95–3.38 | 0.071 |
| Hormonal receptors | | | |
| Unknown | 1.00[a] | | |
| Positive | 0.96 | 0.65–1.43 | 0.851 |
| Age | | | |
| ≤65 years | 1.00[a] | | |
| >65 years | 1.34 | 0.83–2.16 | 0.234 |

[a]Reference values.

**Table 3.** Cumulative incidence rates of first failure events

| | First failure incidence (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 year | | 5 year | | 10 year | | |
| | Ctrl | TAM | Ctrl | TAM | Ctrl | TAM | *P* value |
| Local relapse alone | 21 | 5 | 25 | 8 | 31 | 16 | 0.011 |
| Distant relapse alone | 22 | 15 | 25 | 22 | 25 | 32 | 0.387 |
| Distant + local relapse | 2 | 5 | 4 | 5 | 4 | 7 | 0.348 |
| Death/second cancer | 6 | 3 | 7 | 5 | 10 | 7 | 0.541 |

Ctrl, control; TAM, tamoxifen.

TAM might have a trophic effect in a subset of premenopausal breast cancers by elevating circulating estrogens [12].

Premenopausal women with ILRR fulfilling the inclusion criteria of this study had a very good prognosis. In the control arm of the study, the risk of death was only 10% at 3 and 5 years. This occurred despite the fact that 40% and 45% of the patients had already experienced a further relapse at the respective time points. This excellent survival outcome might reflect good treatment options for these patients or the fact that premenopausal control patients mainly experienced further local reappearance of the

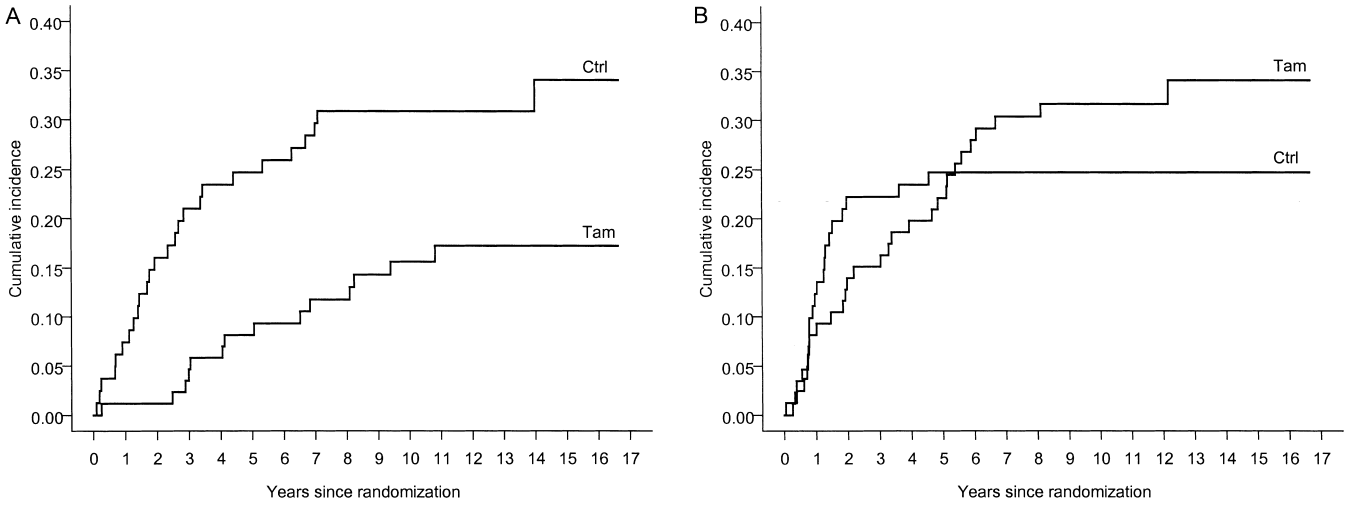


**Figure 2.** Cumulative incidence analysis of site of first relapse. (**A**) Local failure; (**B**) distant failure. Ctrl, control; Tam, tamoxifen.

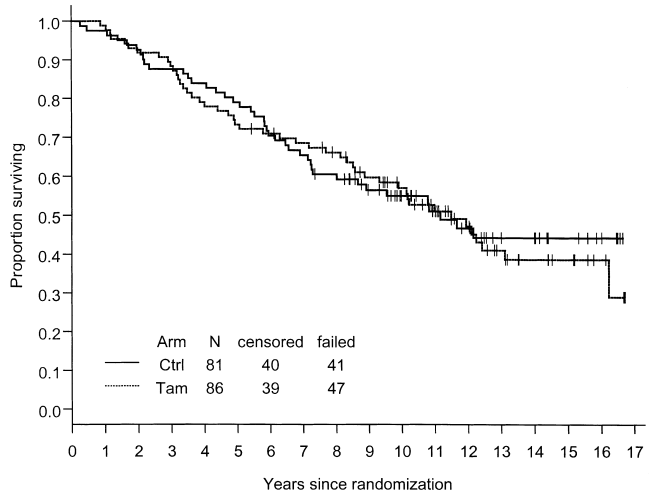


**Figure 3.** Overall-survival by treatment. Ctrl, control; Tam, tamoxifen.

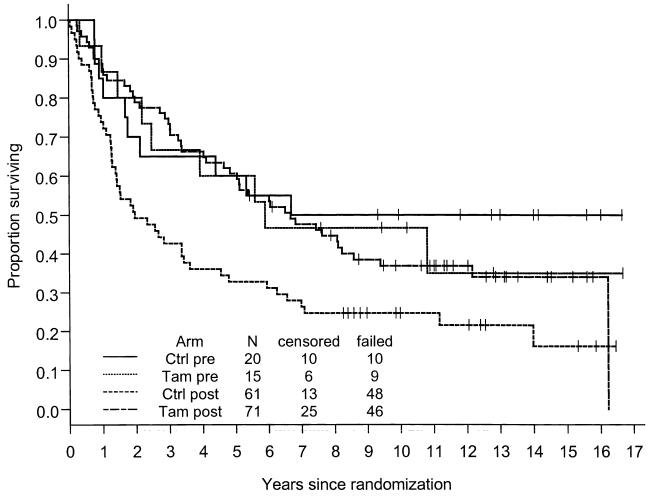


**Figure 4.** Disease-free survival of the study population according to treatment group and menopausal status. Ctrl pre, premenopausal control; Tam pre, premenopausal tamoxifen; Ctrl post, postmenopausal control; Tam post, postmenopausal tamoxifen.

tumor and not distant metastases. Indeed, six patients suffered from another local relapse, two patients experienced both a local recurrence and distant metastases, and no patients developed distant metastases alone during the observation period of the study. These results are not in accordance with the general observation that young age is a poor prognostic factor in patients with breast cancer [13–15]. Rather, they indicate that premenopausal women presenting with ILRR as first relapse site and fulfilling the good prognosis criteria defined in our study represent a favorable prognosis selection of breast cancer patients.

In general, ILRR patients with hormone-sensitive disease represent a favorable subgroup of women relapsing after mastectomy for breast cancer. Our results indicate that ~40% of these patients experience long-term disease freedom after receiving local treatment and TAM. Even without systemic treatment, 30% of patients are free from further local and distant relapses. This observation is in accordance with recently published series on ILRR demonstrating long-term relapse-free survival figures in the range of 30%–40% [16–18]. This is in contrast to the commonly held notion that almost all patients with ILRR eventually develop distant metastases [1]. A possible explanation for this apparent discrepancy is the fact that we, as others, in reporting favorable outcomes [17, 18], were selecting for patients with good prognoses. The selection criteria of our study, such as ER positivity or a DFI of >12 months and small volume disease in case of unknown receptor status, were confirmed in other studies as important prognostic factors for the outcome of ILRR [17–20].

The observation that most patients with ILRR develop distant metastases [1] has been taken as evidence that ILRR is rather a marker for metastatic disease than an isolated relapse site and thus should not be approached with a curative intent. However, in contrast to this nihilistic approach, recent data indicate that ILRR itself can serve as a source of distant metastases, which should

**Table 4.** Multivariate analysis of overall survival

| Variable | Hazard ratio | 95% confidence interval | *P* value |
|---|---|---|---|
| Treatment | | | |
| Surgery + radiotherapy | 1.00[a] | | |
| Surgery + radiotherapy + tamoxifen | 0.90 | 0.58–1.39 | 0.624 |
| Disease free interval | | | |
| ≤12 months | 1.00[a] | | |
| >12 months | 0.37 | 0.19–0.72 | 0.003 |
| Primary tumor size | | | |
| <2 cm | 1.00[a] | | |
| ≥2 cm | 1.24 | 0.74–2.08 | 0.411 |
| Pretreatment adjuvant chemotherapy | | | |
| Yes | 1.00[a] | | |
| No | 1.16 | 0.63–2.13 | 0.633 |
| Nodal involvement (primary tumor) | | | |
| Negative | 1.00[a] | | |
| Positive | 1.53 | 0.86–2.73 | 0.150 |
| Menopausal status (first relapse) | | | |
| Premenopausal | 1.00[a] | | |
| Postmenopausal | 1.62 | 0.85–3.07 | 0.142 |
| Skin lesion (first relapse) | | | |
| No | 1.00[a] | | |
| Yes | 1.83 | 0.89–3.75 | 0.099 |
| Nodal involvement (first relapse) | | | |
| No | 1.00[a] | | |
| Yes | 2.66 | 1.31–5.41 | 0.007 |
| Hormonal receptors | | | |
| Unknown | 1.00[a] | | |
| Positive | 1.23 | 0.78–1.95 | 0.368 |
| Age | | | |
| ≤65 years | 1.00[a] | | |
| >65 years | 2.11 | 1.24–3.57 | 0.006 |

[a]Reference values.

be eradicated as soon and as radically as possible. Fortin et al. showed, in ILRR patients, that the rate of distant metastases peaked at 5–6 years compared with a peak incidence at 2 years for patients without local relapse [21]. This observation is conceivable considering the notion that the later incidence peak represents metastases originating from ILRR as their source. Thus, the early and complete eradication of ILRR seems to be an important goal in achieving maximum cure rates.

Nowadays most patients with ILRR fulfilling the good prognosis criteria of our study have already experienced prolonged adjuvant treatment with TAM for primary breast cancer. The results of studies comparing aromatase inhibitors with TAM or megestrol acetate in hormone-responsive metastatic breast cancer have clearly shown that aromatase inhibitors are still effective in TAM-pretreated patients [22–25]. For ILRR patients fulfilling the poor-risk criteria defined in our study, the question of the value of combination chemotherapy is still of great relevance. The International Breast Cancer Study Group, in collaboration with the Breast International Group, has initiated a study comparing chemotherapy with local treatment alone in patients with locoregional recurrence of breast cancer (IBCSG Trial 27; http://www.ibcsg.org/pub_trials_open27-02.shtml).

## Appendix

Institutions contributing patients to this study included: Kantonsspital, St Gallen (B. Thürlimann, H. J. Senn); Ospedale San Giovanni, Bellinzona (F. Cavalli, M. Varini); Kantonsspital, Basel

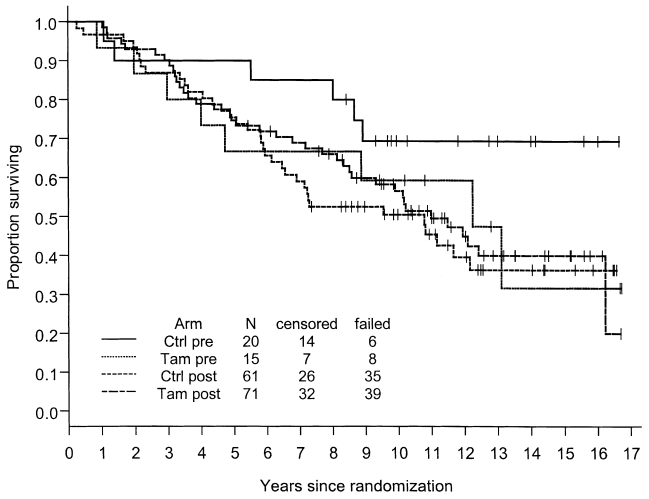


**Figure 5.** Overall-survival of the study population according to treatment group and menopausal status. Ctrl pre, premenopausal control; Tam pre, premenopausal tamoxifen; Ctrl post, postmenopausal control; Tam post, postmenopausal tamoxifen.

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