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Original Paper

Prognosis after Treatment for Loco-regional Recurrence after Mastectomy or Breast Conserving Therapy in Two Randomised Trials (EORTC 10801 and DBCG-82TM)

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The aim of this study was to investigate and compare the prognosis after treatment for loco-regional recurrences (LR) after (modified) radical mastectomy (MRM) or breast conserving therapy (BCT), in terms of overall survival and time to subsequent LR, in patients originally treated in two European randomised trials. In EORTC trial 10801 and DBCG trial 82-TM, 1,807 patients with stage I and II breast cancer were randomised to receive MRM or BCT from 1980 to 1989. All patients with a LR in these trials were analysed for survival and time to subsequent LR after salvage treatment. Of these, 133 patients had their LR as a first event, the majority within 5 years after initial treatment. The prognostic significance for survival and time to subsequent LR after salvage treatment was analysed in uni-, and multivariate analyses for a number of original tumour- and recurrence-related variables. After salvage treatment of LR after MRM or BCT, actuarial survival curves and the actuarial loco-regional control curves were similar. The 5-year survival rates were 58% and 59% and the 5-year subsequent loco-regional control rates 62% and 63%, respectively. In a multivariate analysis, pN category ($P = 0.03$), pT category ($P = 0.01$) and vascular invasion ($P = 0.02$) of the primary tumour were the only independent prognostic factors for survival, whereas extensive LR ($P < 0.001$), interval ≤ 2 years ($P < 0.002$) and pN+ at primary treatment ($P = 0.004$) were significant predictive factors for time to subsequent LR. The type of original treatment (MRM or BCT) did not have any prognostic impact. It is concluded that the survival and time to subsequent LR after treatment for an early loco-regional recurrence after MRM or BCT was similar in these two European randomised trials. This suggests that both after MRM and BCT an early LR is an indicator of a biologically aggressive tumour; early loco-regional relapse carries a poor prognosis and salvage treatment only cures a limited number of patients, whether treated by MRM or BCT originally.

Key words: breast cancer, randomised trials, loco-regional recurrence, salvage treatment, multivariate analysis
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INTRODUCTION

PATIENTS WITH a loco-regional recurrence (LR) after (modified) radical mastectomy (MRM) are known to have a grim prognosis. Studies report 5-year survival rates from 35 to 50% and 10-year survival rates from 18 to 34% [1–8]. However, there is some controversy about the prognosis of patients with a loco-regional recurrence after breast conserving therapy (BCT). A number of series claim a good prognosis after salvage mastectomy with 5-year survival rates of 79–84% [9–12]. Others report 5-year survival rates of 34–50% [13–16]. This discrepancy may, in part, be due to selection differences or follow-up time differences between the various series. Alternatively, loco-regional relapses after MRM or BCT could be the expression of different biological events.

In the early 1980s the EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group both started a randomised trial to investigate the efficacy of BCT, as compared with MRM in stage I and II breast cancer; EORTC 10801 and DBCG-82TM [17, 18]. In both trials BCT consisted of wide tumour excision, axillary clearance, 50 Gy whole breast irradiation and a boost to the tumour bed. The main difference between the trials was that in the DBCG-82TM trial a pre-randomisation procedure according to Zeelen was used, whereas in the EORTC 10801 trial a randomisation procedure after informed consent was applied. The trials both ran for 6 years and accrued 902 and 905 patients, respectively. The first analyses revealed no significant differences between MRM or BCT in either loco-regional control or survival [17, 19]. In the initial analysis of EORTC trial 10801 the outcome of salvage treatment for the 85 patients with a LR appeared to be similar for patients with a LR after BCT or MRM [19]. A long-term follow up analysis of both trials is currently being undertaken.

Since both trials were randomised phase III trials, the characteristics of both original treatment groups (MRM and BCT) were similar with respect to initial prognostic factors. Thus, any differences in prognosis after salvage treatment are unlikely to be the result of selection bias. However, such differences might be due to different causes, if LR after MRM or BCT would be the expression of biologically different events. Moreover, potential differences in prognosis could be due to a difference in the efficacy of the salvage treatment for a LR after either of the original treatments. In theory, a salvage mastectomy for a breast recurrence after BCT could lead to better tumour control than radiation therapy with or without tumour excision for a LR after MRM. Although there are obviously differences in salvage treatment procedures between both groups, the cohort of patients with a LR in these randomised trials can be considered optimal to study potential differences in prognosis following salvage treatment for a LR after MRM or BCT.

Table 1. *Types of loco-regional recurrence (LR)*

MRM	($n = 67$)
Skin single	35
Skin multiple	8
Diffuse	3
Local + regional	4
Regional only	17
BCT	**($n = 66$*)**
Breast (TR or MM)	30
Breast (elsewhere)	13
Diffuse	5
Local + regional	8
Regional only	9

MRM, modified radical mastectomy; BCT, breast conserving therapy; TR, true recurrence; MM, marginal miss. *Type of LR not stated in 1 patient.

The purpose of the present study was to examine the prognosis after salvage treatment for LR in patients originally randomised to receive MRM and BCT to investigate if there was a difference between the treatment groups and to study prognostic factors for the outcome following salvage therapy in terms of overall survival and time to subsequent loco-regional relapse. It must be emphasised that it was not the purpose of the current analysis to evaluate the efficacy of various types of salvage treatment.

PATIENTS AND METHODS

EORTC trial 10801 included 902 patients, entered by eight institutes over a 6-year period (1980–1986) [18]. Of these, 880 were eligible and evaluable. Due to a 2:1 randomisation procedure in the early phase of the trial there were slightly fewer ($n = 424$) patients in the MRM group than in the BCT group ($n = 456$). DBCG trial 82TM accrued 905 randomised patients from 1983 to 1989, entered by 20 institutes. Due to the Zeelen prerandomisation procedure 797 patients received the treatment to which they were randomly assigned. Details concerning the groups and the treatments in both trials are described elsewhere [17–19]. In 1995, an external review and a pathology review was undertaken for all patients reported to have suffered any kind of recurrence, and for those for whom no follow-up report had been received for longer than 1 year. There were no major differences in the overall results of both trials. It was therefore considered justified to analyse the outcome after salvage treatment of a loco-regional recurrence for both trials together. One hundred and twenty-four patients in EORTC trial 10801 and 92 patients in DBCG trial 82TM had suffered a loco-regional recurrence. In 68/880 (7.7%) and 65/797 (8.2%) patients, respectively, the LR occurred as a first event, that is, at least 3 months before the discovery of distant metastases. This 3-month period was chosen because it was considered long enough to perform a staging procedure after discovery of a loco-regional recurrence and discover eventual distant metastases. The subgroup of patients with a loco-regional failure in whom no distant metastases were discovered is the most interesting in terms of the possibility of salvage treatment with curative intent. Therefore, these 133 patients form the basis of the current report.

The majority of loco-regional recurrences were local, on the chest wall (69%) or in the breast (72%), respectively (Table 1). In the BCT group, breast recurrences were classified according to the definition of Recht and associates [20] as: ''breast (true recurrence (TR) or marginal miss (MM))'' or ''breast (elsewhere)''. Supraclavicular recurrences were considered distant metastases and excluded, according to the UICC classification rules [21]. Salvage treatment was given with curative intent in the majority of patients. This treatment consisted mainly of radiotherapy with or without excision in the MRM group and salvage mastectomy (or wide local excision) with or without radiotherapy in the BCT group (Table 2). Adjuvant systemic therapy was given to 26

Table 2. Types of salvage treatment

MRM	($n=67$)
RT ± excision*	48
RT + major surgery*	3
Excision*	13
Systemic only	3
BCT	**($n=66$)**
Mastectomy ± RT*	48
Excision ± RT*	10
RT only	2
Systemic only	5
No treatment	1

MRM, modified radical mastectomy; BCT, breast conserving therapy; RT, radiotherapy. *With or without 'adjuvant' systemic treatment.

patients in the MRM group (39%) and in 18 in the BCT group (27%). It must be emphasised that it was not the intention of the current analysis to evaluate the effect of different types of salvage treatment. The subgroups would be too small to be able to show any relevant differences. Besides, the choice of salvage treatment type was strongly dependent upon the type and extent of recurrence, thus creating a potential bias. Median follow-up time after salvage treatment for the group of 133 patients with a LR as a first event was 74 months.

Age at diagnosis (≤ 45 years versus >45 years), Original UICC [21] cT category (T1 versus T2), pT category (pT1 versus pT2), pN category (pN− versus pN+), presence or absence of extensive *in situ* component (EIC) and presence or absence of vascular invasion (VI) in the original tumour were the clinical and pathological variables tested. To categorise the LRs in both treatment groups in a comparable manner, the extent of the recurrence was defined as limited if single and ≤ 3 cm, and extensive if >3 cm, multiple and/or diffuse. Other variables examined were interval from randomisation to first LR (≤ 2 years versus >2 years) and original treatment (MRM versus BCT).

The endpoints of this study were overall survival from salvage treatment and time to subsequent LR. The time to first LR by treatment group (MRM versus BCT) and survival and subsequent local control data were analysed according to the product-limit method of Kaplan and Meier [22]. In the actuarial subsequent local control curve, all events, whether or not they occurred after the appearance of distant metastases were taken into account. Survival curves were compared using the logrank test [23]. All variables described were analysed in univariate analysis. The independent prognostic significance of these variables was tested using a stepwise proportional hazard regression analysis described by Cox [24]. These analyses were performed on the group of 133 patients with a LR as a first event. The analyses were basically performed using the date of salvage treatment as a starting point. To investigate the possibility of biased results through a systematic earlier occurrence of the first recurrences in one of the treatment groups, the same analyses were performed with the original randomisation date as a starting point, omitting interval to first recurrence as a variable. A separate analysis was performed for both original treatment groups (MRM and BCT) to investigate the possibility of a difference in prognostic factors after either treatment.

RESULTS

Time to first recurrence

The first loco-regional recurrences occurred earlier in the MRM group as compared with the BCT group (Figure 1). This difference was statistically significant ($P=0.02$). The mean difference was 1.2 years.

Survival

Overall, 65/133 (49%) patients with a LR as a first event died. The actuarial survival curves for the MRM and BCT groups (Figure 2) were similar; 5-year survival rates being 58% in the MRM group and 59% in the BCT group. In univariate analysis pN category, vascular invasion, pT category, interval to LR, extent of LR and cT category were significant prognostic factors for survival after salvage treatment (Table 3). In multivariate analysis only pT category, pN category and vascular invasion appeared to be independent prognostic factors, whereas interval to first LR showed a trend (relative risk 1.74, $P=0.07$) (Table 4).

The univariate analysis of survival with the randomisation date as a starting point showed pN category ($P<0.001$), vascular invasion ($P<0.001$) and extent of LR ($P=0.04$) to be

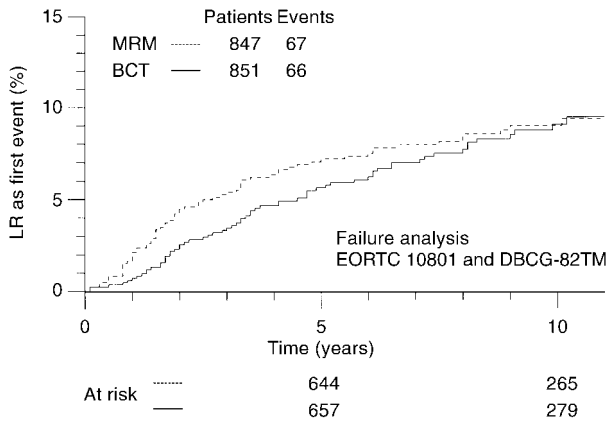

Figure 1. Actuarial time to loco-regional recurrence (as a first event) by original treatment group (MRM versus BCT) for the 1677 patients in trials EORTC 10801 and DBCG-82TM. Patients at risk at 5 and 10 years indicated. MRM, modified radical mastectomy; BCT, breast conserving therapy.

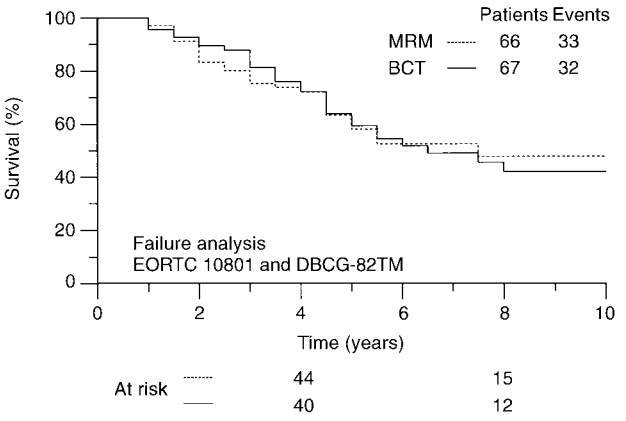

Figure 2. Actuarial overall survival from salvage treatment by original treatment group (MRM or BCT). Patients at risk at 4 and 8 years indicated. Abbreviations as in legend to Figure 1.

Table 3. Univariate analysis for overall survival after salvage treatment

Variable	Overall survival		
	Number of patients	5-year actuarial rate %	*P* value
Original treatment group			
MRM	67	58	0.73
BCT	66	59	
cT category			
T1	56	66	**0.03**
T2	58	48	
pT category			
pT1	86	69	**0.009**
pT2	40	40	
pN category			
pN−	86	68	**0.003**
pN+	44	44	
Extensive *in situ* component			
Absent	102	57	0.89
Present	14	*	
Vascular invasion			
Absent	65	69	**0.005**
Present	56	49	
Age at diagnosis			
≤ 45	26	52	0.14
> 45	107	60	
Extent LR			
Limited	93	61	**0.03**
Extensive	36	48	
Interval to first LR			
> 2 years	76	69	**0.02**
≤ 2 years	57	47	

MRM, modified radical mastectomy; BCT, breast conserving therapy; LR, loco-regional recurrence. *Insufficient number of patients at risk to give a reliable estimate at 5 years. Significant *P* values indicated in bold.

prognostic factors. In multivariate analysis only vascular invasion (hazard ratio 2.52; $P = 0.001$) and pN category (hazard ratio 2.42; $P = 0.001$) remained significant. Original treatment (MRM or BCT) also showed no significance in these uni- and multivariate analyses.

The separate analyses per treatment group showed that interval to first LR, pT category and pN category appeared to be the most important prognostic factors in the MRM group, whereas pN category was the only significant factor in the BCT group (Table 5).

Time to subsequent loco-regional recurrence

Of the 133 patients with a LR as a first event, 46 developed a subsequent LR (35%). The actuarial curves of the MRM and BCT groups showed no difference (Figure 3), actuarial rates at 5 years being 62% in the MRM group and 63% in the BCT group. It is noteworthy that all subsequent LRs occurred within 5.5 years after salvage therapy. In univariate analysis, a number of factors seemed of importance for predicting the local outcome after salvage treatment, particularly pN category, interval to first LR, extent of first LR , pT category and vascular invasion (Table 6). In the multivariate model, the extent of LR, interval to first LR and pN category were independent predictive factors (Table 4).

With respect to subsequent local control, the univariate analysis with the randomisation date as a starting point showed pN category ($P < 0.001$), extent of LR ($P = 0.002$) and vascular invasion ($P = 0.03$) to be significant predictive factors. In the multivariate analysis, extent of LR (hazard ratio 3.81; $P < 0.001$), pN category (hazard ratio 3.49; $P < 0.001$) and vascular invasion (hazard ratio 2.45; $P = 0.006$) all remained significant. Original treatment group (MRM versus BCT) showed no significance whatsoever.

The separate analyses per treatment group showed interval to first LR and extent of LR to be independent predictive factors in the BCT group and pT category and pN category in the MRM group (Table 7).

DISCUSSION

Whilst the poor prognosis of patients with a LR after MRM is well established [1–8], there is some controversy in the literature about the prognosis and salvage possibilities for patients with a LR after BCT. A number of studies have shown that an ipsilateral breast tumour recurrence is a predictor of distant metastases, implying a poor prognosis [16, 25–28]. Other series reporting on local, loco-regional or only regional recurrences after BCT also show a poor prognosis after salvage treatment [13–15, 20, 28]. This is in line with our findings that the prognosis after salvage treatment for LR after BCT and MRM is equally poor. In contrast, some reports have reported good results from salvage mastectomy [9–12, 30]. The discrepancy between these reports and the present study is in part explained by the fact that reports on salvage mastectomy take into account only the subgroup of patients with an operable breast parenchyma recurrence, which forms approximately 75% of all LR [9, 10, 12, 30]. Furthermore, follow-up after salvage treatment was relatively short in some of these reports [10–12]. In the present study, salvage mastectomy was the treatment of

Table 4. Multivariate analyses for overall survival and time to subsequent loco-regional recurrence (LR) after salvage treatment

Variable	β	*P* value	Relative risk*
Overall survival			
pT category	0.70	0.01	2.02
Vascular invasion (present versus absent)	0.70	0.02	2.02
pN category (pN+ versus pN−)	0.60	0.03	1.83
Interval to first LR (≤ 2 years versus > 2 years)	0.55	0.07	1.74
Time to subsequent LR			
Extent of LR (extensive versus limited)	1.22	< 0.001	3.40
Interval to first LR (≤ 2 years versus > 2 years)	1.06	< 0.002	2.88
pN category (N+ versus N−)	0.92	0.004	3.40

21 patients with no information on one or more of the variables were excluded from the analysis. *Relative risks are presented only for the retained variables ($P < 0.1$).

Table 5. *Multivariate analyses for overall survival for both treatment groups (MRM and BCT) separately*

Variable	β	*P* value	Relative risks*
MRM group			
pT category (pT1 versus pT2)	0.90	0.02	2.46
pN category (N+ versus N−)	0.84	0.03	2.32
Interval to first LR (≤ 2 years versus > 2 years)	1.13	0.02	3.10
BCT group			
pN category (N+ versus N−)	0.86	0.03	2.36
Vascular invasion (present versus absent)	0.75	0.07	2.11

*Relative risks are presented only for the retained variables ($P < 0.01$).

choice in 48/66 (73%) of the patients with a LR after BCT, but the other 27% of patients were also included in the analysis. Moreover, with a 5-year actuarial survival rate of 61% (95% confidence limits 53–69%), the survival of these 48 patients was not different from that of the BCT group patients as a whole, or of the MRM group patients.

The uniformly reported prognostic factor for survival after salvage treatment for a LR after MRM is interval to first LR [1–8, 30, 31]. Size or extent of the recurrence is also mentioned as a significant factor by some authors [3, 5, 6], and site (chest wall or axilla only versus both) by one [4]. Prognostic factors for survival after salvage treatment for LR following BCT are less well established. Most studies addressing this issue investigated only selected groups of relapsing patients considered suitable for salvage treatment with curative intent (i.e. salvage mastectomy for breast recurrences) [9, 15, 16, 30], or performed only a univariate analysis [9, 14, 30]. Nevertheless, interval to first local recurrence seems the most important factor [9, 14, 16, 30]. Extent and site (''true recurrence or marginal miss'' versus ''elsewhere'') of the recurrence are also found to be prognostic factors [9, 15], as well as nodal involvement [33]. Despite the methodological problems of comparing results of (obviously different) salvage treatment types for LR after MRM or BCT, there seems to be a remarkable similarity in prognostic factors for survival after the different initial treatments in the literature. This suggests that loco-regional relapses after both types of primary treatment may be the result of similar biological events. In our study the predictive factors for subsequent loco-regional recurrence seem different for both the original treatment categories (pT and pN categories for the MRM group, and interval to first LR and extent of LR in the BCT group; Table 7). Similarly, the prognostic factors for survival seem different in both original treatment groups (Table 5). The difference in predictive factors for subsequent loco-regional control may reflect a difference in the requirements of the obviously different salvage treatments in both groups, rather than a true difference in causality of the loco-regional recurrences in both groups. However, a slight difference in causality of the loco-regional recurrences after BCT or MRM cannot be excluded. One should be cautious in the interpretation of these results, since the numbers of patients and the numbers of events are very small.

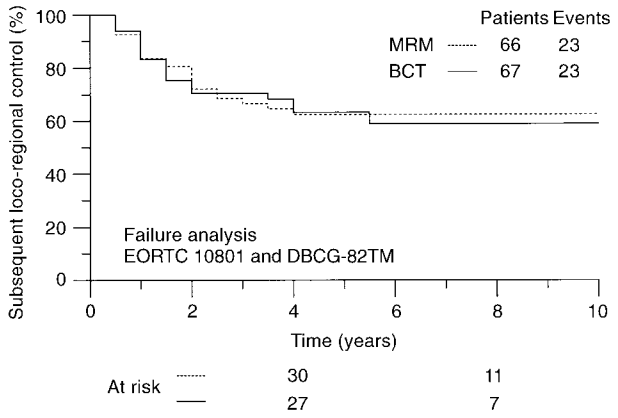

Figure 3. Actuarial time to subsequent LR from salvage treatment by original treatment group (MRM or BCT). Patients at risk at 4 and 8 years indicated. Abbreviations as in legend to Figure 1.

Table 6. *Univariate analysis for time to subsequent loco-regional recurrence (LR) after salvage treatment*

	Time to subsequent LR		
Variable	Number of patients	5-year actuarial rate %	*P* value
Original treatment group			
MRM	67	62	0.87
BCT	66	63	
cT category			
T1	56	62	0.96
T2	58	60	
pT category			
pT1	84	70	**0.004**
pT2	40	45	
pN category			
pN−	86	74	**0.001**
pN+	44	41	
Extensive *in situ* component			
Absent	102	63	0.94
Present	14	*	
Vascular invasion			
Absent	65	72	**0.03**
Present	56	52	
Age at diagnosis			
≤ 45	26	54	0.21
> 45	107	65	
Extent LR			
Limited	93	70	**0.002**
Extensive	36	43	
Interval to first LR			
> 2 years	76	74	**0.001**
≤ 2 years	57	48	

MRM, modified radical mastectomy; BCT, breast conserving therapy.
*Insufficient number of patients at risk to give a reliable estimate at 5 years. Signaificant *P* values indicated in bold

Table 7. Multivariate analyses for subsequent loco-regional control for both treatment groups (MRM and BCT) separately

Variable	β	*P* value	Relative risk*
MRM group			
pT category (pT1 versus pT2)	1.41	0.001	4.12
pN category (N+ versus N−)	1.16	0.008	3.18
BCT group			
Interval to first LR (≤ 2 years versus > 2 years)	1.57	< 0.001	4.82
Extent of LR (extensive versus limited)	1.54	0.001	4.69

MRM, modified radical mastectomy; BCT, breast conserving therapy. *Relative risks are presented only for the retained variables ($P < 0.1$).

One factor probably represents a true difference between the MRM and BCT groups and might have an impact on prognosis. In the series of Kurtz and associates [9, 30] and Haffty and colleagues [15, 28], addressing breast recurrences only, site of relapse (''true recurrence or marginal miss'' versus ''elsewhere'') was found to be a prognostic factor which is closely correlated with interval to first LR. Early breast recurrences tend to occur in the same quadrant as the original tumour. Late recurrences (having a much better prognosis) occur elsewhere in the breast. The same time pattern was found by others [33, 34]. The cut-off point between early and late in these series is between 4 and 5 years. These studies strongly suggest that late breast recurrences should be considered as new primary tumours—thus, a separate entity within the recurrence group with the same prognosis as a patient with a completely new primary tumour. The difference in time to first recurrence between the treatment groups (Figure 1) in the present study might be a reflection of this difference. The difference in predictive factors, particularly 'interval to first recurrence' between the MRM and BCT groups may be an indication of the same. However, the number of breast recurrences ''elsewhere in the breast'', as well as the number of breast recurrences beyond 5 years is too small to draw conclusions.

The difference in time to first failure between the original treatment groups (Figure 1) may have an additional cause. It is possible that a breast parenchyma recurrence after BCT is more difficult to detect than a (sub)cutaneous recurrence after MRM. This effect might cause a systematic delay in detection of LR after BCT. It may, therefore, in part be the cause of the detected difference.

In the multivariate analysis, extent of recurrence and interval to first LR were the main predictive factors for time to subsequent LR, together with original pN category. In the multivariate analysis for overall survival, pT category, pN category and vascular invasion were the only independent significant factors, interval to first LR showing a non-significant trend. Both interval to first recurrence and extent of recurrence, however, showed a significant survival difference in the univariate analysis. They are probably too closely correlated to vascular invasion and pN category to show independent prognostic significance. Vascular invasion is known to be a strong prognostic factor, both for local control and survival after primary treatment [16]. It was analysed as a prognostic factor for the outcome of salvage treatment in only one of the above-mentioned salvage treatment studies [10] in which it showed no significance.

In the present study there was no difference in prognosis after salvage treatment, nor in terms of overall survival or subsequent local control for patients suffering a LR following MRM or BCT. As previously discussed, potential prognostic differences between the groups could result from different biological factors leading to a LR, or from a difference in effect of salvage treatment. It is unlikely that differences between the groups in salvage treatment (principally high-dose radiotherapy in the MRM group and surgery in the BCT group) would have a major impact on survival that would compensate for a more aggressive biological behaviour of one of the groups. Thus, the similarity of the groups in terms of survival and time to subsequent LR strongly suggests that a LR after either treatment is the expression of the same biological process. It must be emphasised that this only applies to early local recurrences (occurring within 5 years after original treatment). It is quite possible that late recurrences after BCT comprise a separate category of patients with a much better prognosis after salvage treatment.

In conclusion, in this comparison of prognosis after treatment of patients with an early loco-regional recurrence after modified radical mastectomy or breast conserving therapy, the survival and time to subsequent LR after salvage treatment was equal. This strongly suggests that early LR after MRM and BCT basically have the same biological characteristics. A patient with an early LR after BCT appears to have an equally poor prognosis as a patient with an early LR after MRM.

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