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Adjuvant Chemoimmunotherapy with LMF + BCG in Node-negative and Node-positive Breast Cancer Patients: 10 Year Results

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Abstract—*A total of 254 patients with stages T1–3a/N0–1/M0 operable breast cancer were randomized to either surgery alone or surgery plus adjuvant chemoimmunotherapy (LMF + BCG). Ten-year results are presented for RFS (relapse-free survival) and OAS (overall survival) in the whole patient population as well as in the most important menopausal and nodal subgroups.*

LMF + BCG significantly increased RFS in the whole patient population as well as in node-positive women. The earlier impressive RFS and OAS gains for node-negative patients were fading after 5 and 8 years respectively, leaving marginal trends in favour of the LMF + BCG treated women. Node-positive patients treated with LMF + BCG continue to demonstrate a marginal gain in RFS up to 10 years. This gain is nearly exclusively expressed in postmenopausal node-positive women, an observation which can be made in the node-negative patient group as well. Despite the still continuing increase in RFS, no OAS benefit was observed for node-positive women with LMF + BCG at any time of the study.

Dose still remains a critical factor in cancer therapy. However, at 10 years of follow-up, a full dose of LMF (≥90%) during the six cycles no longer affects OAS favourably.

There was no indication of any adverse long-term toxicity of LMF + BCG in our study after a median follow-up of 10 years, especially no increase of second tumours.

In the node-negative patient population, the presence or absence of intramammary lymphatic infiltration seems to be a significant prognostic factor within this nodal subgroup.

INTRODUCTION

BECAUSE medium- to long-term survival expectancy, and thus mortality, for patients with operable breast cancer has remained essentially unchanged during the past 40–50 years in most countries, increasing numbers of clinical adjuvant studies have emerged during the past decade in node-positive breast cancer patients [1–3]. However, when initiating the first adjuvant breast cancer trial in Eastern Switzerland 14 years ago, histologically node-negative women were also incorporated (on a stratified basis) for the following three reasons:

1. Our regional observation of a lower relapse-free survival (RFS) and overall survival (OAS) in node-negative patients than usually cited in the literature.
2. Node-negative patients with truly 'minimal postoperative tumour cell burden' were assumed to constitute an ideal and completely curable population to test the present concept of adjuvant systemic chemotherapy because to date at least 25–30% of node-negative patients worldwide present recurrent, mostly incurable disease within 5–10 years after mastectomy.
3. The choice of a well tolerated adjuvant regimen without potential hair loss, chemical cystitis or significant gastrointestinal upset (LMF). Immunostimulation with bacillus Calmette-Guérin (BCG) was added to the chemotherapy chlorambucil (Leukeran®) + methotrexate + fluorouracil (LMF) on the basis of earlier claims that BCG skin scarifications would counterbalance the immunodepressive effects of cytotoxic treatment and potentially prolong RFS or OAS, or both. In this paper, 10-year results (median duration of follow-up) are reported.

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PATIENTS AND METHODS

Between 1974 and 1977, a total of 254 patients with stages T1–3a, N0–1 and M0 operable breast cancer were randomized to either surgery alone

Table 1. Treatment plan used as adjuvant chemoimmunotherapy in breast cancer patients (OSAKO Protocol SG 06/74). Regimen A: modified radical mastectomy alone; regimen B: modified radical mastectomy followed by combined chemoimmunotherapy within 14–30 days after surgery

Duration	Drugs per os	Dosage/body wt <70 kg	Dosage/body wt >70 kg	Frequency of application
2 weeks	CLB	6 mg	8 mg	daily
	MTX	5 mg	7.5 mg	3 days/week
	FU	50 mg	750 mg	1 ×/week
2 weeks pause				
Intermittent therapy as described above is continued for a period of 6 months				
From 26 weeks onwards, repeat BCG skin scarification every 4 weeks for the next 3 years or until relapse occurs				

Abbreviations: OSAKO: Ost-Schweizerische Arbeitsgemeinschaft für Klinische Onkologie: CLB: Leukeran; MTX: methotrexate; FU: fluorouracil; BCG: bacillus Calmette-Guérin.

Table 2. Distribution of prognostic factors of 240 evaluable patients in adjuvant study OSAKO SG 06-74. Only general nodal status (N−, N+) was stratified prior to randomization in both treatments

Sub(group)	All patients	Surgical controls	Surgery + LMF + BCG
All (N− and N+)	240	123	117
N−	122	65	57
N+	118	58	60
N+ (1–3)	80	38	42
N+ (≥4)	38	20	18
T1–2a	218	112	106
T3a	22	11	11
Pre-/perimenopausal	126	63	63
Postmenopausal	114	60	54
N− pre-/perimenopausal	62	31	31
N− postmenopausal	60	34	26
Median age at surgery	55.3	56.7	53

Reasons for exclusion (14 patients): 1 second tumour at randomization; 4 randomization error; 5 staging error; 2 refusal; 2 lost to follow-up.

(modified radical mastectomy without adjuvant radiotherapy) or the same type of surgery + six cycles of oral LMF, followed by monthly skin scarifications with BCG (Glaxo strain) up to relapse or 2 years (Table 1). The details of the study design, patient selection and follow-up programme have been reported previously [4, 5]. No hormone receptor data were available during the years of patient accrual. At the time of the 10-year analysis in January 1986, 240 of 254 randomized patients (94%) could be fully evaluated. The two treatment groups were well balanced regarding known risk factors, as shown in Table 2. Statistical comparisons were performed using the chi-square test and a computer program of the statistical centre of the Swiss Group for Clinical Cancer Research (SAKK), Bern/Switzerland (PD Dr. W. Berchtold).

RESULTS AT 10-YEAR MEDIAN FOLLOW-UP

Ten-year results are presented graphically, for RFS and OAS in the whole patient population (N− and N+), as well as in the most important menopausal and nodal subgroups. In contrast to the basic nodal status (N−, N+), menopausal status and nodal substatus were not stratified prior to randomization for surgery alone or surgery + LMF + BCG, thus limiting statistical conclusions and cross-study comparisons in these patient subgroups. Premenopausal patients included also perimenopausal women (up to 5 years after last menses or 55 years of age).

Whole patient population (N+ and N−)

Figure 1 shows a highly significant distinction in RFS and OAS between the N− and N+ global study patient population ($P < 0.001$). Whereas after 35 months post mastectomy, 50% of the N+ patients have relapsed and after 88 months 50% died, the 50% limit (median) has not yet been reached, even after 10 years for both RFS and OAS, in the N− population. The 10-year survival (OAS) was 40% for N+ and 73% for N− patients.

In Figure 2, premenopausal and postmenopausal women are compared for RFS and OAS. There is no statistically significant difference between the two groups in the whole patient population.

Figure 3 compares the two treatments in the whole patient population (N+ and N− patients). After 10 years, there is still a significant increase in RFS for patients treated with LMF + BCG ($P = 0.05$). The increase of median RFS for LMF + BCG treated patients is approx. 38 months. This gain in RFS is, however, not transmitted into increased OAS after 10 years ($P = 0.16$). If one now studies the survival curve representing 10 years of follow-up (with all patients being followed at least 8 years), there is no more significant difference in OAS between the two groups of treatment in the whole population, although the trend in favour of LMF + BCG persists. This is shown by the *P*-values at different times, calculated now from the 10-years curve (P at 3 years = 0.16, at 5 years $P = 0.11$, at 7 years $P = 0.40$, at 8 years $P = 0.53$, at 9 years $P = 0.29$, at 10 years $P = 0.16$).

Figure 4 shows a significant gain in RFS in favour of LMF + BCG treated patients in the subgroup of all *postmenopausal* patients ($P = 0.02$). At the time of 10 years evaluation, there is no evidence of the curves merging. This gain in RFS seems to transform now into a significant gain in OAS ($P = 0.04$). The numerical gain of +26% in RFS and +18% in OAS is clinically remarkable. There

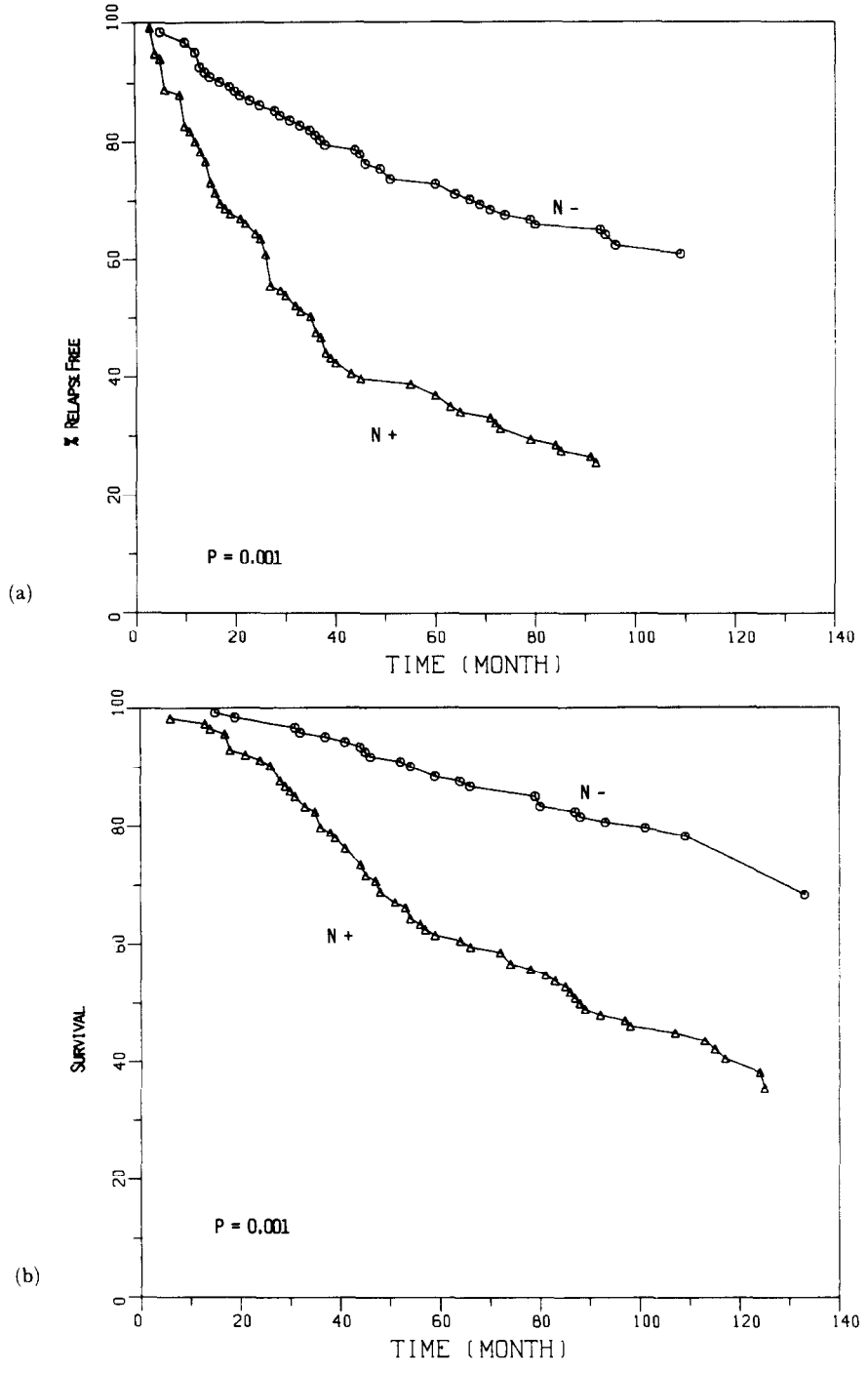


Fig. 1. Prognostic influence of initial nodal status, all patients and both treatment arms combined. (a) Relapse-free survival, (b) overall survival.

is no significant difference between the LMF + BCG treated patients and the surgical control either in RFS or OAS in the *premenopausal* patient group. An initial gain in RFS, which was never transmitted into an OAS benefit, disappeared after 3–4 years.

Subgroup of N− patients

Figure 5 shows the evolution of the difference in RFS in both treatment groups of N− patients. Following an impressive divergence of the curves in favour of LMF + BCG treated women during the first 3–4 years, this difference vanished after 5–6 years. However, at 10 years, there is still a tendency for the curves to differ, which has stayed the same since the 6th year of follow-up. A marginal gain in RFS can be postulated for the N− patient group treated with LMF + BCG over the whole period of observation ($P = 0.19$). At 10 years, the gain in RFS is still 9% (54% vs. 63%).

An earlier, impressive appearing difference in OAS between the LMF + BCG treated N− patients and the surgical controls has, in actual fact, never

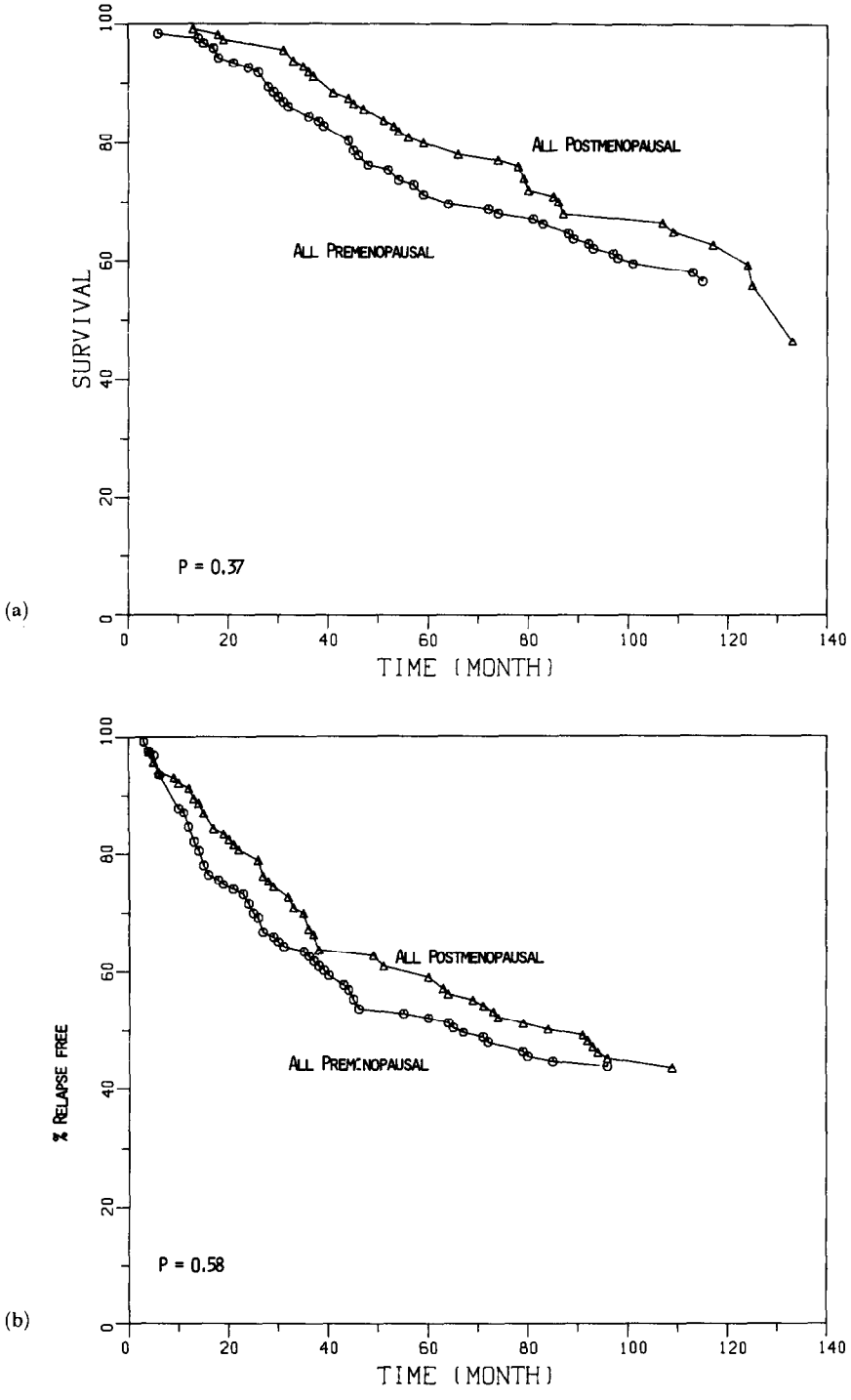
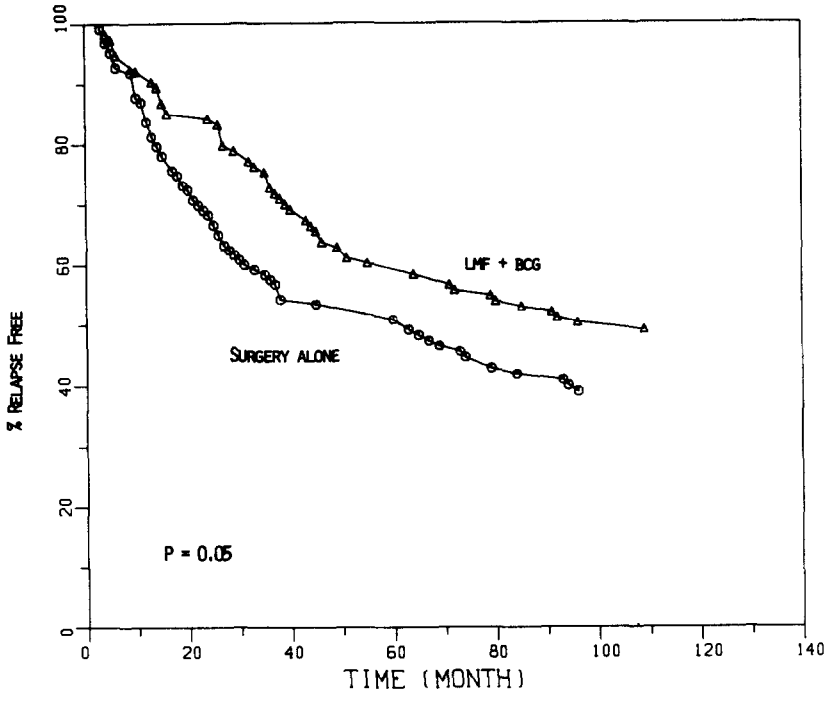


Fig. 2. Missing prognostic influence of menopausal status at surgery. (a) Relapse-free survival, (b) overall survival.



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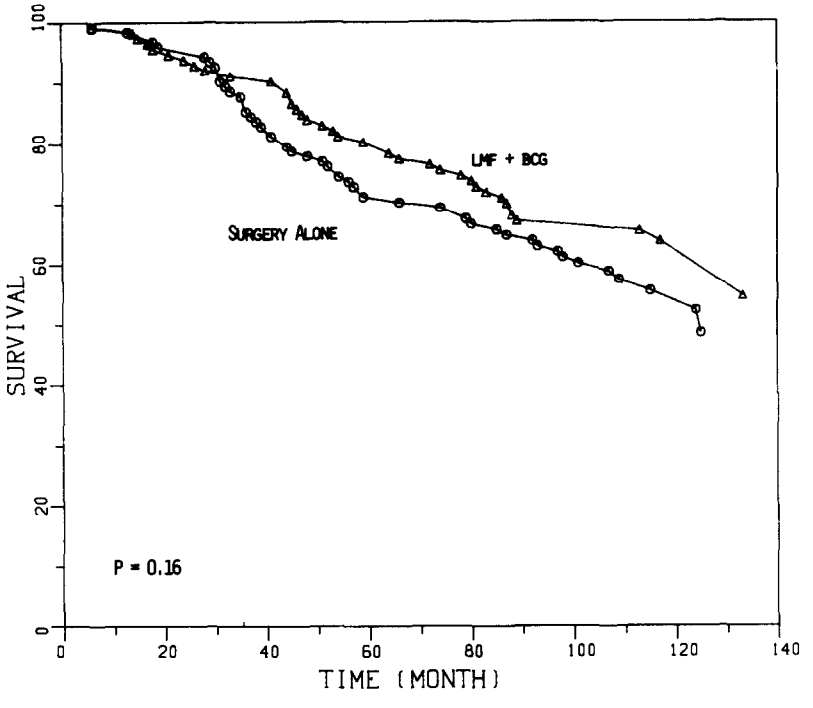

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Fig. 3. All patients. (a) Relapse-free survival, (b) overall survival.

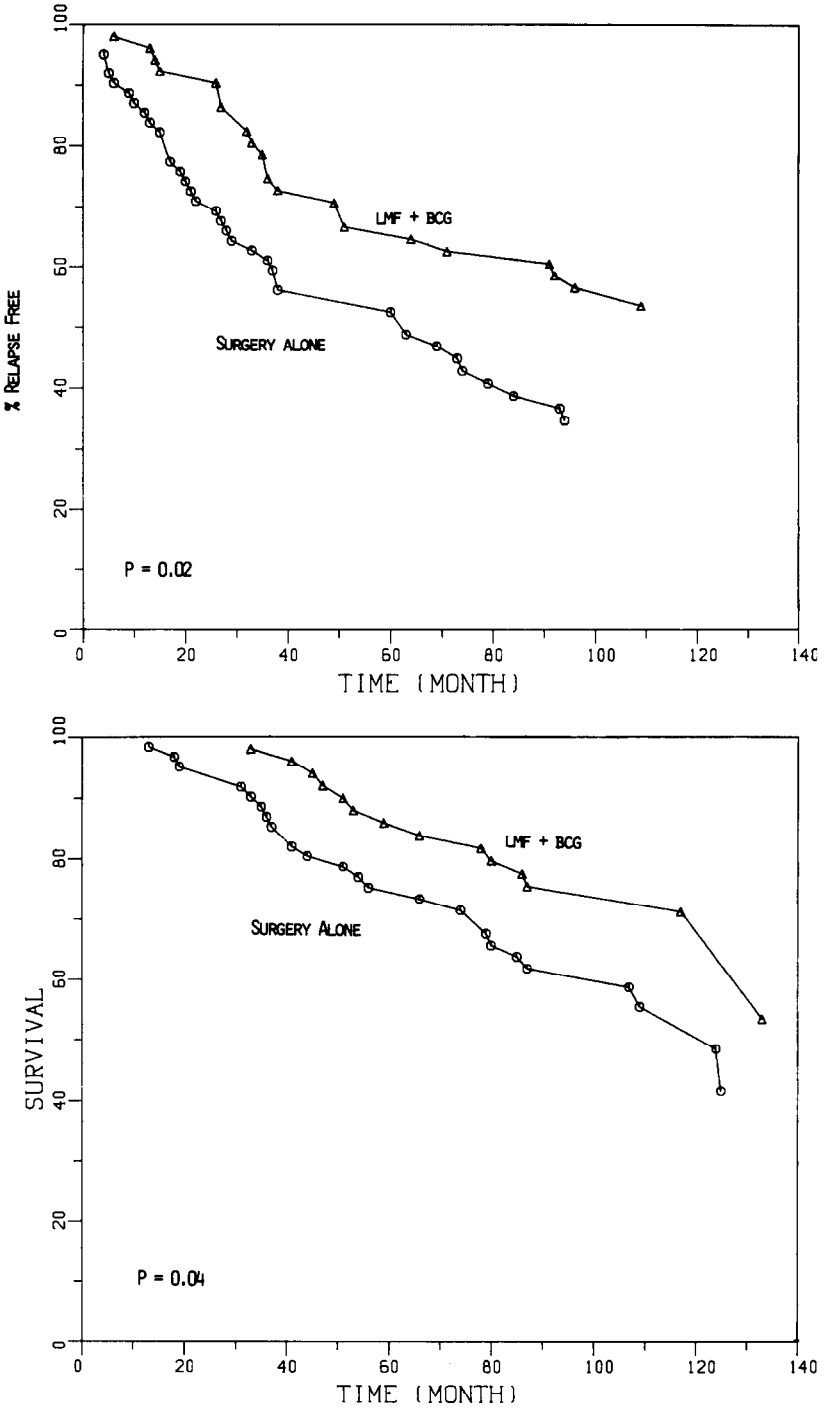

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Fig. 4. All postmenopausal patients. (a) Relapse-free survival, (b) overall survival.

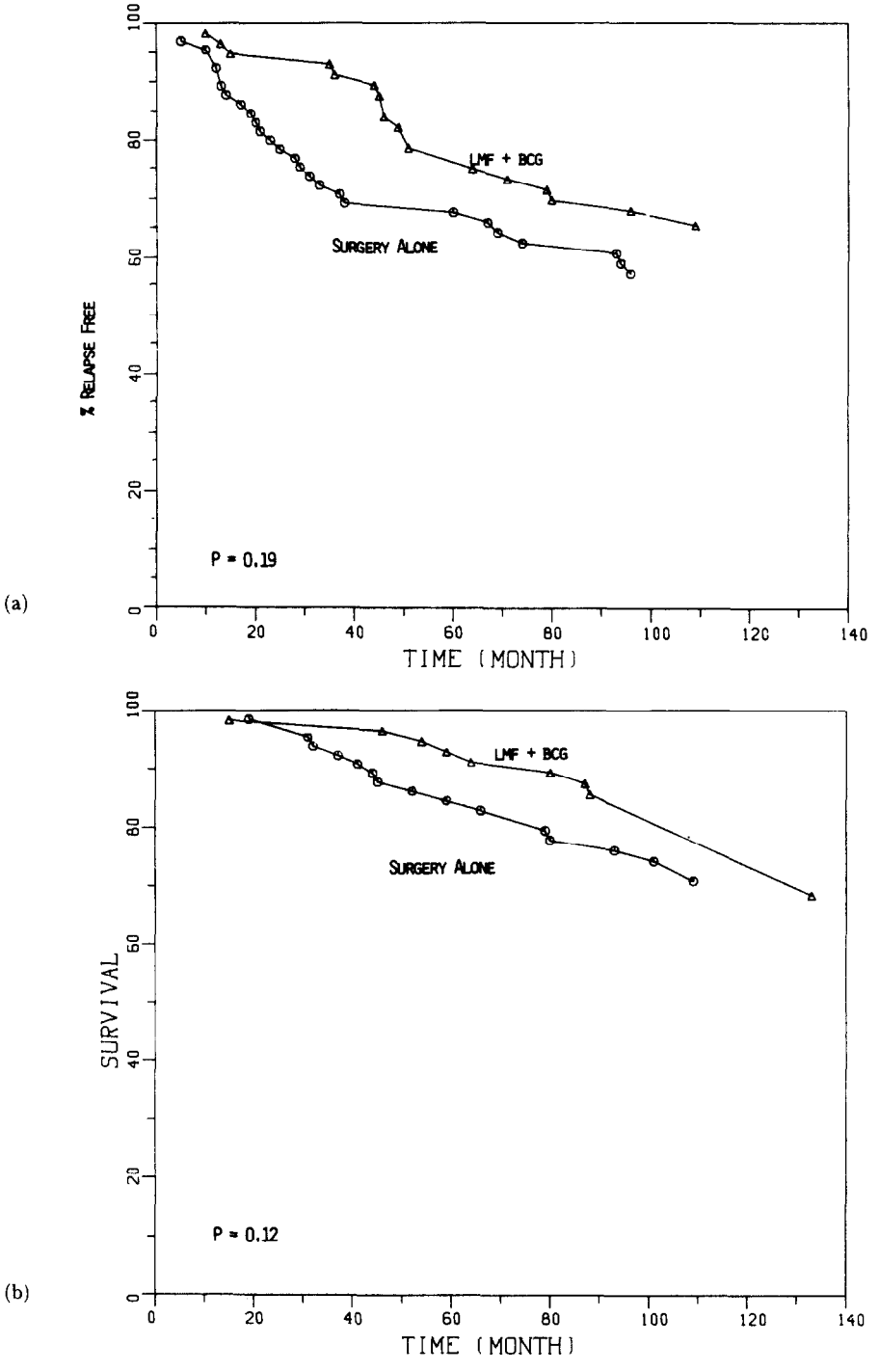


Fig. 5. All node-negative patients. (a) Relapse-free survival, (b) overall survival.

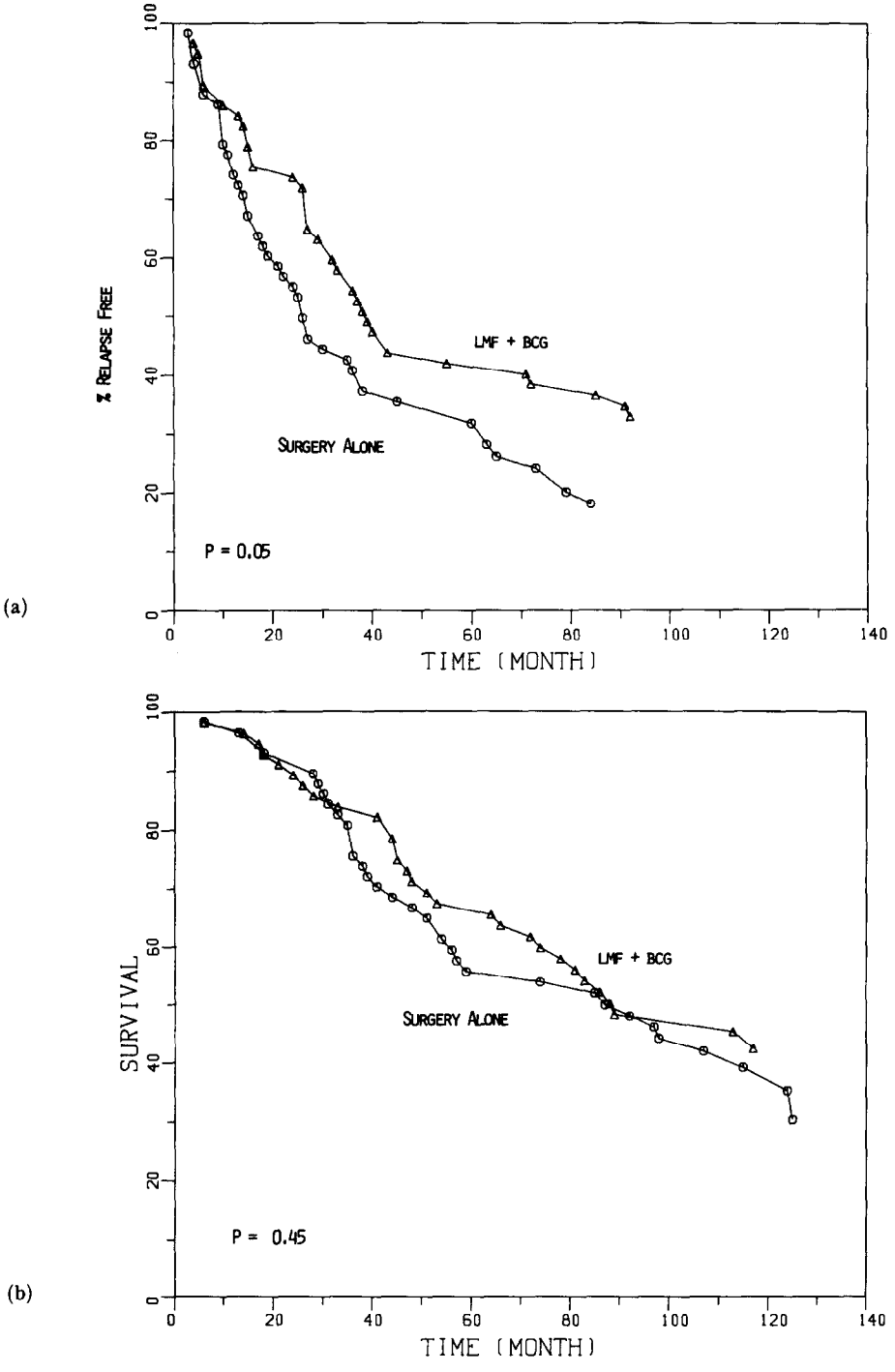


Fig. 6. All node-positive patients. (a) Relapse-free survival, (b) overall survival.

been significant, which can be shown by calculating the *P*-values for the different times retrospectively from the 10-years curves: *P* at 3 years = 0.19, at 5 years $P = 0.14$, at 7 years $P = 0.09$, at 8 years $P = 0.20$, at 9 years $P = 0.27$, at 10 years $P = 0.12$). Our latest evaluation shows only a tendency of the curves to differ up to 7 years, which then fades again. However, the numerical gain in OAS at 10 years is still 5% (68% vs. 73%).

Looking at menopausal subgroups of the N− patients, the prolonged, but now fading, advantage of increased RFS and marginally increased OAS was mostly due to the effect of LMF + BCG in the *postmenopausal* sub-population. However, at 10 years, there is no significant difference between the two treatments, either for RFS or OAS in this subgroup (*P* for RFS = 0.25, 60% vs. 48% relapse free, for OAS $P = 0.10$). Further statistical conclusions are limited by the small number of patients in those non-stratified menopausal subgroups.

Subgroups of N+ patients

In N+ patients, showing 'no benefit' with LMF + BCG during the first 3 years, a persistent and rather increasing difference in RFS in favour of LMF + BCG treated women emerged after the 4th year, which is still increasing after 10 years ($P = 0.05$, Fig. 6). However, this late benefit in RFS never translated into an increased OAS ($P = 0.45$).

As in N− patients, the increasing difference in RFS in favour of LMF + BCG treated patients in the N+ patient population is due to the postmenopausal patient subgroup, which not only seems to benefit in RFS ($P = 0.01$), but also shows a tendency to gain in OAS ($P = 0.09$). As mentioned above, results of these non-stratified subgroups have to be interpreted carefully.

All favourable effects of LMF + BCG in node-positive patients were seen in women with one to three positive axillary nodes (*P* at 10 years = 0.07 for RFS and 0.19 for OAS). In highest risk women (≥4 nodes), there was virtually no difference between the two treatment regimens observed, either for RFS or OAS.

There is a strong indication in N− patients that the presence or absence of intramammary lymphatic infiltration in the mastectomy tissue influences the prognosis remarkably (Fig. 7). A significant advantage was observed in OAS for patients without lymphatic infiltration ($P = 0.03$). The difference in RFS is not significant (largely due to population size), but also these curves show a tendency to diverge ($P = 0.08$).

Treatment intensity

At 10 years, the earlier evidence suggesting that a full total dose (≥90%) during the six cycles of LMF positively affected OAS has meanwhile disappeared (0.28, Fig. 8). However, the two groups of treatment intensity (≥90% vs. ≤89%) are very imbalanced in numbers and the dose analysis was done retrospectively.

Late toxicity (second tumours)

Metachroneous second malignancies in node-negative and node-positive study patients are shown in Table 3. The application of six intermittent cycles of LMF + BCG does not seem to increase the occurrence of second tumours.

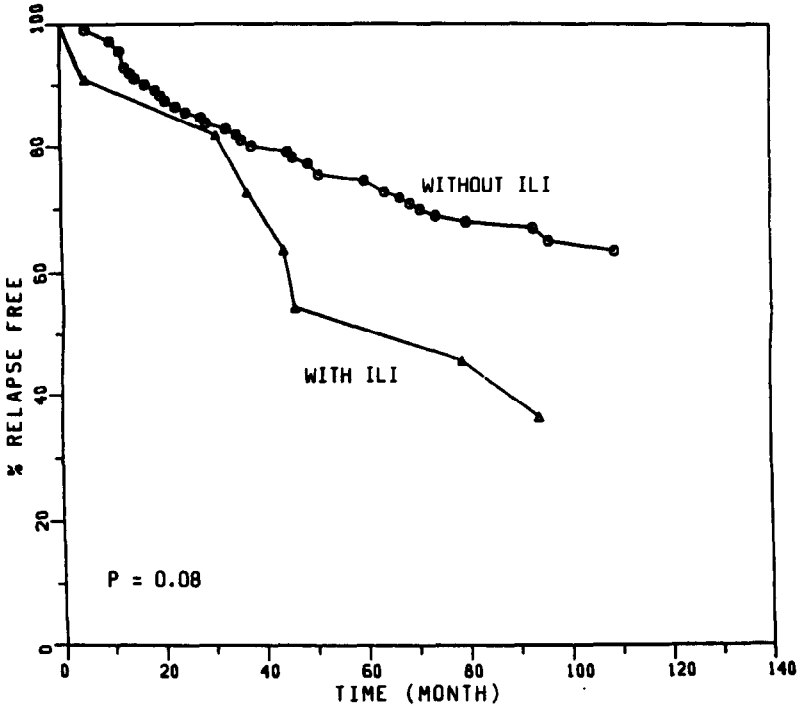
Within the last 4 years, no more second tumours have been observed. Of the total of 13 patients who developed second malignancies, 10 died of the second tumour, two are still alive and only one died from recurrence of her primary breast cancer (in this case, the second tumour was a squamous cell skin cancer).

Table 4 shows the evolution of relapse at 10 years in N− patients. There is no significant difference as to the distribution in categories and sites of first recurrence and to first manifestation of distant metastases with or without adjuvant LMF + BCG.

DISCUSSION

Since the 3rd year of median follow-up, the total group of all study patients, treated with LMF + BCG, continues to show a significant gain in RFS, now up to 10 years median observation time post-mastectomy. Earlier evaluations gave the impression that this RFS difference expressed itself as an OAS gain between the 4th and 7th year. Looking at the curves now, at 10 years follow-up, it becomes evident that this significance of OAS gain has been lost since the 8th year of follow-up. In other words, patients treated with adjuvant LMF + BCG remain relapse-free considerably longer than the surgical control group, but finally, they do not survive significantly longer. A longer relapse-free survival time, however, can also mean a better quality of life [6]. The median gain in relapse-free survival time of 38 months (3 years) for all LMF + BCG treated patients is remarkable. Whether adjuvant chemotherapy later adversely influences subsequent salvage therapy results in the case of tumour relapse still remains controversial [7].

Irrespective of treatment, there is no difference in RFS and OAS between the postmenopausal and premenopausal subgroups, confirming the fact that menopausal status *per se* is not a prognostic factor. Yet these subgroups show a different response to adjuvant treatment with LMF + BCG. It is a constant feature of this trial that postmenopausal women seem to profit preferentially from adjuvant LMF + BCG. This contradicts two studies with melphalan (L-PAM) and cyclophosphamide + methotrexate + fluorouracil (CMF) [8, 9], but is



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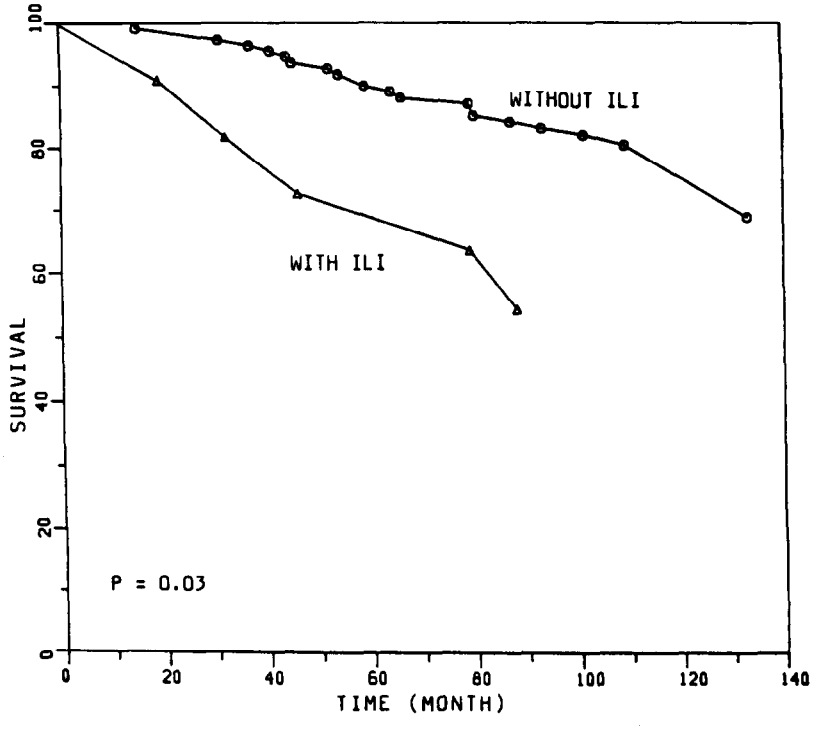

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Fig. 7. Prognostic influence of intramammary lymphatic infiltration (ILI) in node-negative patients at surgery. (a) Relapse-free survival, (b) overall survival.

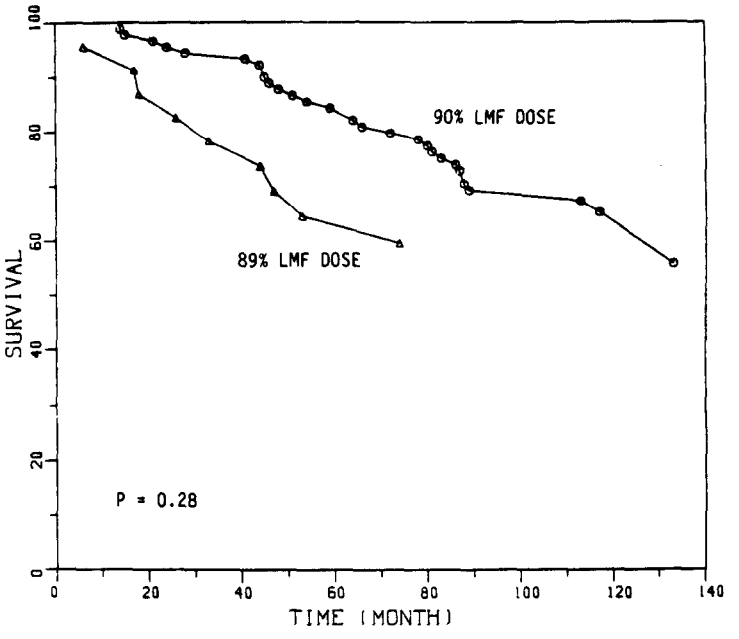

Fig. 8. Correlation of total dose of LMF (≥90% vs. ≤89%) on overall survival of all LMF patients (N− and N+). Non-randomized retrospective comparison.

Table 3. Late toxicity observed in node-negative and node-positive patients with second tumours at 10 years

Surgical controls (n = 58)		LMF + BCG (n = 60)	
Type of neoplasm	No. of patients	Type of neoplasm	No. of patients
N+ patients (n = 118)	58		60
Contralateral breast	2	Bronchus	1
Second tumours:		Corpus uteri	1
Colon + ALL	1	Ovarial + endometrial	1
Parathyroid	1	Epithelial skin	1
Bronchus	1		
Total No. of second tumours	3 (5.1%)		4 (6.6%)
N− patients (n = 122)	65		57
Contralateral breast	1	Contralateral breast	1
Second tumours:		Second tumours:	
Central nervous system	1	Rectum	1
Tonsils	1	Stomach	1
Colon	1		
AML	1		
Total No. of second tumours	4 (6.1%)		2 (3.5%)

ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia.

Table 4. Evolution of 1st relapse site and death at 10 years in N− patients

		Site (1st relapse)		Deaths		
Patients	No.	Locoregional	Distant + mixed	Breast cancer	Other causes	Total
Surgical controls	65	9 14%	18 28%	16 25%	7 11%	23 35%
LMF + BCG	57	8 14%	11 19%	9 19%	6 11%	15 26%

not at all unique. Several current adjuvant breast cancer trials show postmenopausal women benefitting from adjuvant chemotherapy either nearly as much or even more than younger patients [3, 10–13].

Node-negative patients treated with LMF + BCG experienced an impressive RFS increase during the first 3 years of median observation time. However, at 4–5 years of median follow-up, there was a strange accumulation of late relapses among LMF + BCG treated patients. This lends support to the idea that the concept of late, periodic adjuvant consolidation cycles should be clinically explored [14]. However, a marginal gain in RFS can be postulated for the node-negative patient subgroup treated with LMF + BCG over the whole period of observation. Although an earlier appearing gain in OAS for LMF + BCG treated node-negative women is no longer significant at 10 years, a fairly strong tendency towards increased OAS in favour of LMF + BCG remains. This corresponds well with a current adjuvant breast cancer trial showing a significant benefit with adjuvant CMF after 4 years of median follow-up [10, 11].

In our node-negative patients, the presence or absence of intramammary lymphatic infiltration at the time of mastectomy seems to be a significant prognostic factor within this nodal subgroup. Node-negative women without lymphatic infiltration fare significantly better concerning RFS and OAS than patients with this histologic characteristic. This analysis was, however, done retrospectively on non-stratified subgroups in a prospective adjuvant trial, and does therefore not allow for final conclusions. Other studies have been set up especially dealing with this question [15, 16].

Node-positive patients treated with LMF + BCG continue to demonstrate a marginal gain in RFS, as reported since the 5th year of median observation. If analysed in menopausal subgroups, this gain is nearly exclusively expressed in postmenopausal node-positive women, an observation which can be made in the node-negative patient group as well. Due to small patient numbers and non-stratification of menopausal status prior to randomization, we, however, hesitate to attach too much importance to this menopausal subgroup discordance. Despite the still continuing gain in RFS, no OAS benefit was observed for node-positive women treated with LMF + BCG at any time in our study.

Analysis of the relapsing node-negative and node-positive patients showed no significant difference as to the distribution in categories and sites of first recurrence and to manifestation of distant metastases with or without adjuvant LMF + BCG. A more detailed report will be published separately.

Various groups and investigators strongly disagree as to the correlation of adjuvant drug doses administered and patients' prognoses. In our study, the earlier evidence suggesting that a full dose of LMF (≥90%) during the six cycles affected OAS favourably has disappeared after 10 years ($P = 0.28$). Again, we must caution against over-interpretation of data, because this comparison was retrospective and has never been satisfactorily answered in a prospective study. Yet the dose remains a critical factor in cancer therapy and this also seems to be the case for adjuvant treatment situations [3, 17].

There was no indication of any adverse long-term toxicity of LMF + BCG in our study population after a median follow-up of 10 years, especially no increase of second solid neoplasias and (acute) leukaemias. This finding is in agreement with several other adjuvant studies and was summarized recently [9, 18]. As a matter of fact, subsequent contralateral breast cancers were seen primarily and two cases of acute leukaemias (one AML and one ALL) only in the surgical control group of our study. This emphasizes that increased late toxicity data and expectations from other diseases and treatment schedules (such as extensive MOPP chemotherapy and radiotherapy of Hodgkin's disease) should not simply be extended to relatively short-term, intermittant adjuvant chemotherapy for breast cancer.

CONCLUSIONS

On the basis of our present 10 year follow-up data on 240 fully evaluable patients, we tentatively conclude that LMF + BCG (as given in our trial) significantly increased RFS in the whole patient population as well as in node-positive women, especially those who are postmenopausal. LMF + BCG also significantly increased OAS in all postmenopausal patients, which was a constant feature of this trial. Whether—due to its potential benefit and remarkably low toxicity—LMF (given fully orally) + BCG represents a standard option for adjuvant breast cancer therapy outside clinical trials, especially for postmenopausal patients, remains open. The earlier impressive RFS and OAS gains for node-negative patients were fading after 5 and 8 years respectively, leaving marginal trends in favour of the LMF + BCG treated women. We do not think that the addition of long-term BCG scarifications (included in the adjuvant regimen in 1974, at which time it was clinically 'en vogue' to do so) had any beneficial effect. At least there is no remarkable difference in RFS and OAS data in a (non-randomized) cross-study comparison with identically selected node-positive patients of SAKK study 27/76, treated only with adjuvant oral LMF alone [19].

Whether the discordant results in menopausal patient subgroups between this study (with adju-

vant LMF + BCG) and the first Milan study (with adjuvant CMF) are real findings or just statistical artefacts must await maturing results of a head-to-head comparison of LMF i.v. × 6 vs. CMF i.v. × 6 cycles, actually in progress [19]. If proven as effective as and significantly less toxic than CMF in certain patient groups, LMF could become a valuable and more acceptable adjuvant chemotherapy and an alternative to CMF for certain subgroups of operable breast cancer patients.

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