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Review

Current Status and Indications for Adjuvant Therapy in Breast Cancer

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Summary. *1. Modified radical mastectomy is the standard surgical procedure today in most countries. 'Lesser surgery' associated with radiotherapy emerges as an alternative for patients with T_1N_0 lesions.*
2. The potential risk of occult micrometastases is best predicted by careful axillary staging and possibly by the ER status of the primary tumor.
3. Additional risk factors such as tumor size, patient age, menopausal status, and intramammary lymphatic or vascular invasion are less well established and need clarification.
4. Previous studies showed no significant long-term benefit of adjuvant radiotherapy and at best a marginal increase of lifespan by adjuvant castration in patients subjected to radical surgery.
5. Various types of adequately intensive adjuvant chemotherapy resulted in a significant increase of relapse-free survival and probably also overall survival 5–6 years after mastectomy in pre- and possibly also postmenopausal N+ patients.
6. Treatment intensity (full doses) of adjuvant chemotherapy seems to be more critical than treatment duration (CMF × 6 is as good as CMF × 12).
7. Adjuvant chemotherapy with drug combinations is generally more effective than single drugs. No combination so far (if adequate doses are given) is clearly superior.
8. Whether early peri-operative onset of adjuvant chemotherapy or combinations with endocrine measures or cyclic, alternating drug regimens increase effectiveness remains to be shown.
9. Adjuvant chemotherapy in N– patients, though still experimental, appears rewarding.
10. The pattern of first relapse has not been significantly altered by the use of adjuvant chemotherapy. Response rate and duration with secondary treatments are consistent with common experience in metastatic disease.
11. Up to 5–6 years median observation time there is no proof that the risk of second neoplasms is increased by currently used adjuvant chemotherapy regimens.
12. More and highly critical prospective trials are needed to assess not only effectiveness, but also patient tolerance (cost-benefit ratio) of adjuvant therapies in breast cancer.

Introduction

Breast cancer is by far the most frequent tumour affecting women in Western, industrialized countries [20]. One of every 11–15 females will eventually develop this malignant tumor within her adult lifetime, and despite a long history and evolution of therapeutic experience, more than half the patients initially treated by locally 'curative' measures will finally relapse and usually succumb to their disease within 10 years of surgery. As a consequence of this therapeutic stagnation, mortality from breast cancer has never declined during the past decades, despite efforts to increase earlier diagnosis by public education and by increasing use of mammography. On the contrary, mortality from this tumour has slowly increased in many countries (shown in Fig. 1 for Switzerland) since 1900 in all age groups, paralleling the slight increase in breast cancer incidence during the past 70–80 years [51].

It has been widely accepted and documented that local therapy (various types of mastectomy with or without adjuvant radiotherapy) cures breast cancer in less than half of all patients involved [7, 17, 25]. The concept of initially undetectable distant micrometas-

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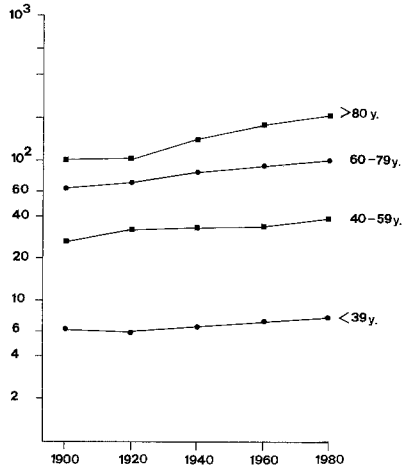

Fig. 1. Slight, but steady increase of age-specific breast cancer mortality in Switzerland from 1900 to 1980 (per 10^5 women in the population). From Van der Linde [51]

tases not only derives from theoretical concepts [41, 45], but is amply substantiated by the fact that even 25%–30% of patients with small primary tumors and no axillary metastases (so called node-negative [N–] cases) eventually relapse and die within 8–10 years after mastectomy [25]. Involvement of the axillary nodes at the time of initial surgery seems to be indicative of the risk category of relapse and survival: if one to three axillary noded are involved, the relapse-free survival (RFS) falls to less than 30% and overall survival (OAS) to around 40% within 10 years of the primary treatment; with more than four nodes involved these prognostic figures are right down to 15%–20%, indicating that breast cancer for many patients is a disease that is impossible to cure by traditional means [23–25, 50]. Although treatment after relapse or overt dissemination with combination of cytostatic drugs and hormones has definitely improved during recent years, there is little hope of a cure after disease recurrence [19, 39].

Since the body of published and orally communicated work about adjuvant treatments in this common disease has mushroomed in the last 10 years, I shall resist the vain temptation to be completely up to date and I shall derive my conclusions only from studies with longer than 3 years of median follow-up, mentioning other more recent and current investigations with premature and often exaggerated data only for the sake of information and to indicate future investigational leads.

Position of Local Therapy 1982

The fact that surgery with or without additional radiotherapy cured only a relatively small fraction of patients with breast cancer, even if extended to supraradical levels with a consequent increase of sequelae [53], has greatly changed the attitude of surgeons towards primary treatment. The Halsted radical mastectomy, initially introduced for locally advanced tumors around 1900, has represented the standard surgical procedure for the past 80 years [29, 35]. The en bloc removal of the primary tumour together with its lymphatics and axillary nodes was indicative of Halsted's belief that the tumour spread contiguoulsy. Although he obviously recognized tumour spread 'which extended from the cranium to the knee', Halsted nevertheless deduced, that 'breast cancer in the broad sense is a local affection' [29]. It was only 60–70 years later, when critical surgeons such as Bernhard Fisher and Michael Baum declared the contrary: 'Breast cancer is a systemic disease until proved otherwise' [3, 23]. Several theoretical and laboratory concepts led to the conclusion that less radical procedures would result in at least the same cure rate, reducing toxicity from surgery and radiotherapy (Table 1). In the 1960s, the NSABP showed in a large trial including more than 1600 node-positive (N+) patients that there was no difference in RFS or OAS when patients were randomized either to Halsted's radical mastectomy or to the modified type of radical mastectomy [22, 26]. During the last decade, data from several French centres aroused the medical profession and especially the lay press, because even less radical surgery (lumpectomy) combined with local radiotherapy was apparently just as well able to cure patients with a small breast cancer lesion as mutilating mastectomy. This concept was subsequently tested in a randomized fashion by the NSABP group and by Veronesi and co-workers at the National Cancer Institute in Milan, who have recently published their 5-year observations in detail: there is virtually no difference between Halsted's radical mastectomy and quadrantectomy plus local radiotherapy with regard to the rate of loco-regional or distant relapses, and RFS and OAS up to 5 years are virtually the same [54]. Results of the NSABP trial are not yet available. It must be emphasized that this type of less aggressive surgery so far applies *only* to patients with very favourable small T_{1-2a} lesions (which may be about one-fifth of the population) and with no clinically involved axillary nodes. For the majority of breast cancer patients, at least in Switzerland, modified radical mastectomy (also called total mastectomy with axillary clearance in the United States) is still the standard form of local therapy today.

What is the indication for *adjuvant radiotherapy* in these 'radically' mastectomized patients? I do not intend to enlarge greatly on this topic, since at least

Table 1. Controlled studies to test the value of 'lesser surgery'

Group (stage)	No. of patients	Treatment	Follow-up	Results
NSABP B-04 (T_{1-3}, N_{0-1}) [26]	1,680	Halsted RM Mod. RM (Total mastectomy + ax. dissection)	6 years	No difference in RFS and OAS
INT Milano (T_1, no palp. ax. nodes) [54]	701	Halsted RM Quadrantectomy (+ ax. diss. + RT + adj. CT in N+)	5 years	Virtually identical RFS and OAS
NSABP B-06 (T_{1-2}, no palp. ax. nodes) [25]	Progr.	Mod. RM (TM) Segm. mastectomy + ax. dissection Segm.-mastectomy + ax. diss. + RT	< 3 years	Not yet available

Data from JAMA 244: 797 (1980) and N Engl J Med 305: 6 (1981)

Table 2. Long-term results of adjuvant radiotherapy in radically operated breast cancer (survival %)

Study	Treatment	5 Years	10 Years
Manchester O	RM	56 >	44 >
	RM + RT postop.	55 >	43 >
Manchester P	RM	61 >	48 >
	RM + RT postop.	57 >	44 >
Edinburgh	RM + Castration	76 >	–
	SM + RT postop. + C	66 >	–
Copenhagen	SRM	67 >	–
	SM + RT postop.	66 >	–
NSABP/USA	RM	62 >	–
	RM + RT postop.	56 >	–
CRC/London	SM	77 >	–
	SM + RT postop.	74 >	–

Data from Stjernsward [46, 47]

six or seven prospectively randomized and several retrospective studies have consistently shown that adjuvant radiotherapy, delivered according to various schemes of fractionation and including serval radiation sources, are unable to significantly delay the occurrence of distant metastases or to prolong OAS (Table 2 and [7, 11, 24, 47]).

This topic has been extensively reviewed several times in recent years. Even if radiotherapists do not like to accept Stjernswärd's conclusion, that adjuvant radiotherapy shortens RFS and OAS in premenopausal patients by long-standing depression of T lymphocyte function [46], they have on the other hand failed to prove any significant benefit for the combined approach, once radical mastectomy is performed [3, 11, 24, 47]. Unnecessary additional treatments, however, should be avoided because of the chronic toxicity (frozen shoulders, radiation skin, lymphoedema, occasional actinic plexus neuritis, etc.) as well as restricted resources. Whether additional radiotherapy as an adjunct to minimal breast surgery or even as primary treatment for breast cancer will be an acceptable alternative to the more extensive surgery now current, remains to be fully investigated.

Rationale for Adjuvant Systemic Treatment, 1982

Besides the above-mentioned clinical findings from previous trials and the analysis of natural history following loco-regional therapy alone, preclinical laboratory data have greatly contributed to the present rationale for adjuvant systemic therapy. Studies in experimental animal tumour models, for example with the C3H mouse mammary tumour, have shown that resection alone and chemotherapy alone cannot eradicate the disease and cure a substantial number of tumour-bearing mice [41]. If, however, the two modalities were combined sequentially – whereby time sequences may be of crucial importance – cure rates of more than 50% were obtained. The elegant work of Skipper and Schabel [41, 45] on cell kill and residual tumour burden became the basis of future clinical trials, substituting for the previous assumption that a short course of adjuvant cytotoxic drug therapy peri- or postoperatively would prevent metastatic dissemination by

killing circulating tumour cells liberated into the bloodstream by surgical manipulations [36]. The present rationale for adjuvant systemic treatment is rather based on the assumptions (a) that occult micrometastases are already present at the time of diagnosis and initial therapy, the proportion depending on risk categories; and (b) that the capacity of local surgery to cure by only removing visible tumour and that of local (superimposed) adjuvant radiotherapy to improve cure rates of breast cancer are limited; and (c) that tumour cell kill occurs according to first-order kinetics (killing of a given percentage instead of a specific number of cells), thus necessitating prolonged, intermittend adjuvant chemotherapy cycles for 6–24 (?) months. There is an absolute requirement for proper and standardized patient selection and statistical analysis, preferably in randomized trials [6].

Results of Early Trials of Adjuvant Chemotherapy

The investigators of the NSABP group with Fisher and the Scandinavian group with Nissen-Meyer were among the first, 15–20 years ago, to pioneer the field of adjuvant chemotherapy in breast cancer [35, 36]. However, some of the studies from this time do not entirely hold up to current clinical and statistical principles and some are hard to interpret [6, 25]. One has to realize however, that at least five of eight published trials with short, peri-operative mono-chemotherapy (with agents such as thio-TEPA, nitrogen mustard, fluorouracil, or cyclophosphamide) resulted in a *decrease of relapse rates* in the adjuvant treatment group, at least for some patient subpopulations. This was associated with improved survival in only two studies. Nissen-Meyer and co-workers recently published their updated 10-year results after a short course of IV cyclophosphamide after mastectomy: there remains a significant increase of RFS and OAS for the treated patients, although there were differences in results between participating hospitals and no clear distinction of prognostic variables such as stratification for axillary node status [6, 36]. The Scandinavian authors, however, insist that beneficial results could only be obtained when adjuvant chemotherapy was given *immediately* after or together with breast surgery, thus preventing postoperative regrowth and early resistance of residual tumour cells. This assumption has to be tested again in current adjuvant trials [33]. If it is correct it would at least protect many patients (and their doctors and health insurance) from having prolonged courses of systemic treatment with its attendant toxicity and costs.

Results of Current Adjuvant Chemotherapy Trials

The advances in palliative control of advanced breast cancer by combination chemotherapy [10, 14, 52] and new concepts of cell killing gained from animal models led to the start of a new generation of carefully controlled breast cancer trials after 1973. A review of seven such trials comparing various adjuvant chemotherapy regimens with surgery alone (radical or modified radical mastectomy) is shown in Table 3. These studies and their results cannot all be described in detail, but recent publications and periodic reviews have appeared in various languages and countries [6, 7, 42]. The first part of Table 3 contains two 'mature' trials sponsored by the National Cancer Institute, Bethesda, USA, one with L-PAM (Melphalan), conducted by the NSABP Group, and the other with CMF (cyclophosphamide + methotrexate + fluorouracil), conducted in Milan by Bonadonna and co-workers [8, 26, 39]. Both clearly demonstrated an increase in RFS at 5–6 years after mastectomy, but only in premenopausal patients, the NSABP trial only in those premenopausal women with three or less positive axillary lymph nodes. Overall survival was improved with borderline significance only in the Milan trial. Two additional randomized trials with surgical controls have been performed since 1974: one done by our group in Eastern Switzerland (OSAKO trial [43, 44]) with a rather low dose and well-tolerated oral LMF (chlorambucil + methotrexate + fluorouracil) used for 6 months and followed by BCG, yielding increased RFS and OAS only in N− patients and not in N+ ones; the other randomized trial was done in Great Britain by the Multicentre Breast Cancer Chemotherapy Group (MBCCG), showing increased RFS and possibly OAS at 4 years by the use of CFVM chemotherapy (Table 3) (T. Wheeler 1981, personal communication).

Additional non-randomized adjuvant trials by Cooper et al. with vigorous adjuvant CMFVP, by the Houston investigators from MD Anderson Hospital with FAC + BCG and by the Arizona group with AC (with or without radiotherapy) all showed increased RFS and OAS over historical surgical controls after 5–8 years of median follow-up after mastectomy [2, 12, 16]. Except for the Milan and the NSABP trials, all other studies showed concordant results in *pre- and postmenopausal* women; the reason for this difference is not entirely elucidated at present time, but will be discussed later with regard to *treatment intensity*. In summary, in six of these seven controlled trials with either a concomitant, randomized, or carefully selected historical surgical control group, a significant increase in RFS after 4–8 years of median

Table 3. Results of adjuvant chemotherapy in breast cancer (N+) patients (Surgical control studies)

Institution group	No.	Adjuvant RX (chemo)	Follow-up (years)	Essential findings
Milano [7]	386	CMF × 12 vs RC	6	↑ RFS and ?OAS pre-m.
NSABP [26]	348	P × 24 vs RC	5	↑ RFS, but not OAS in pre-m., 1–3 nodes
OSAKO [45]	241	LMF + BCG vs RC	5	No ↑ of RFS + OAS in N+[a]
MBCCG [57]	247	CFVM vs RC	4	↑ RFS, ?OAS[a]
Cooper [16]	100	CMFVP vs HC (± RT)	8	↑ RFS and OAS only in non-irrad. pts[a]
Houston [12]	222	FAC + BCG vs HC	5	↑ RFS and OAS, BCG??[a]
Arizona [2]	98	AC (± RT) vs HC	5	↑ RFS and OAS, no neg. effect of RT[a]

RC, Randomized surgical controls; HC, historical surgical controls
[a] No difference in results between pre- and postmenopausal patients

Table 4. Results of adjuvant breast cancer trials comparing different chemotherapy regimens or duration (N+ patients)

Group	No.	Therapy post mastectomy	Follow-up (years)	Essential findings
Milan [8, 48]	325	CMF × 12 vs × 6	4	No diff. in RES/OAS both effective
SAKK [31]	386	LMF × 6 vs × 24	3	No diff. in RFS/OAS (ineffective in N+)
COG [18]	254	P vs CMFV	5	CMFV better than P in (post-m. > 50 years)
NSABP [26]	348	P vs PF	3	PF better than P
SWOG [28]	334	P (± RT) vs CMFVP	3	CMFVP better than P
CALGB [49]	449	CMF vs CMF + MER vs CMFVP (± RT)	4	CMFVP better than CMF (in post-m., no benefit from MER)
Mayo Clinic [1]	166	P vs CFP vs CFP (± RT)	3	CFP better no adverse effect of RT

follow-up was observed, which nominally was in the range of 15%–25% more patients alive and disease-free at 5 years after surgery. In some studies a definite increase of overall survival remains to be demonstrated, but can be expected with great probability from the extrapolation of present RFS data. The reasons why our own OSAKO trial with LMF failed to show increased RFS and OAS in N+ cases may include: (1) relatively low dose schedule; (2) oral administration of all three drugs; and (3) only 6 months of chemotherapy together with (1) and (2) [43, 44].

Table 4 summarizes data of an additional group of current breast cancer trials, which did not primarily compare the new adjuvant approach to surgical controls, but compared the effectiveness of *different* chemotherapy regimens or of different treatment durations in N+ patients. In a most appropriate second trial, the Milan group showed convincingly that six monthly cycles of (full dose) CMF was identical with twelve cycles of CMF in their effect on RFS and OAS at 4 years [8, 48]. The Swiss national trial SAKK 27/76 compared 6 months of oral LMF with 24 months of the same treatment: there is no difference in results after more than 3 years of median follow-up [31]. In five more adjuvant trials done by the Central Oncology Group (COG), the NSABP Group, the South-West Oncology Group (SWOG), the Cancer and Leukemia Group B and the Mayo Clinic, randomized comparisons uniformly demonstrated superiority of combination chemotherapy regimens over mono-chemotherapy with L-PAM (four studies) or a 'lesser' combination (CMF, one study) in N+ patients [1, 18, 26, 28, 49]. One may therefore conclude that combinations such as CMF, CMFV, or CMFVP of limited duration are preferable to long-term use of single drugs. A survey of currently used adjuvant programmes is listed in Table 5.

A very interesting approach, which may somehow modify the design of future adjuvant breast cancer trials, was recently demonstrated by Jones and others of the Arizona group: they pooled data from various breast cancer trials, carefully stratified as to risk groups, and compared (1) RFS and OAS data from trials without randomized surgical controls against their 'natural data base' and (2) the RFS and OAS data of various adjuvant regimens against each other [30]. It may thus be possible to assess the relative merits of various chemotherapy or other adjuvant treatments. Present data also show that no adjuvant regimen yields definitely better RFS data after 4–6 years, not even adriamycin-containing regimens such as AC (or FAC), which still should not be used outside carefully controlled trials in view of their potential long-term cardiotoxicity [4, 55] (Fig. 2).

Table 5. Examples of adjuvant chemotherapy used in breast cancer

Acronym	Cytostatics (combinations)	Administration	Duration (months)
P (AM) [26]	Phenylalanine-Mustard	Days 1– 5 PO every 6 weeks	24
PF	PAM	Days 1– 5 PO every 6 weeks	24
	Fluorouracil	Days 1– 5 IV	
CMF (P) [5]	Cyclophosphamide	Days 1–14 PO	
	Methotrexate	Days 1+ 8 IV every 4 weeks	6; 12
	Fluorouracil	Days 1+ 8 IV	
	(Prednisone)	Days 1– 7 PO	
LMF [44]	Chlorambucil	Days 1–14 PO	
	Methotrexate	Days 1+ 8 PO every 4 weeks	6; 24
	Fluorouracil	Days 1+ 8 PO	
CVFM[a]	Cyclophosphamide	Days 1+ 8 IV	
	Vincristine	Days 1+ 8 IV every 4 weeks	6
	Fluorouracil	Days 1 IV	
	Methotrexate	Days 8 IV	
AC [2]	Adriamycin	Days 1 IV	
	Cyclophosphamide	Days 2– 6 PO every 4 weeks	3–8 (cycles)
FAC [12]	Fluorouracil	Days 1+ 8 IV	
	Adriamycin	Days 1 IV every 4 weeks	24
	Cyclophosphamide	Days 1 IV	

[a] T. Wheeler, 1981, personal communication
[b] Change to CMF after total dose of 300 mg/m^2

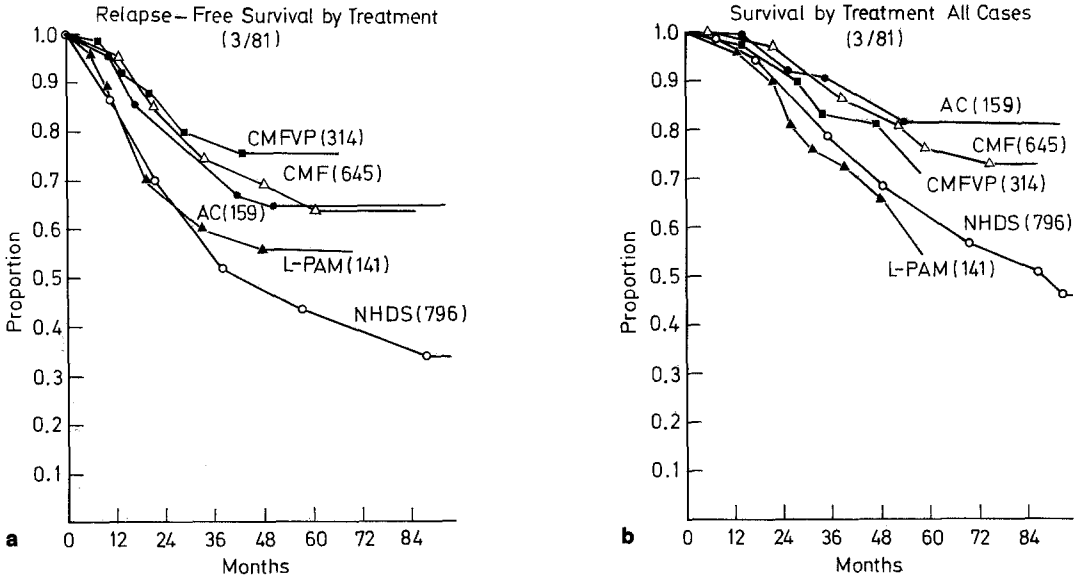

Fig. 2a and **b.** Relapse-free survival (**a**) and overall survival (**b**) of breast cancer patient groups from various adjuvant studies, compared with the natural history data base [30]. Courtesy of Dr. S. E. Jones, University of Arizona Cancer Center, Tucson, USA. For abbreviations used for adjuvant regimens see Table 5. NHDB, natural history data base

Correlation Between Treatment Intensity and Effectiveness

The discordant behaviour of pre- and postmenopausal women in the NSABP L-PAM trial and the Milan trial with CMF raised the question as to whether the beneficial effect of adjuvant chemotherapy in premenopausal patients was finally mediated by *endocrine* changes, induced by "chemical amenorrhoea" in as many of 70% of women receiving CMF × 12 cycles [40]. However, Bonadonna for the Milan trial and Fisher for the NSABP study showed

convincingly that there was no significant difference in 5-year RFS whether amenorrhoea occurred or not, either under or over 40 years of age [8, 26, 40].

Retrospective analysis of the drug doses received in the Milan trial disclosed that postmenopausal women received significantly lower doses of CMF than younger patients, and there was a rather close correlation between dose levels and the rate of 5-years RFS: patients receiving nearly full doses of CMF fared significantly better than those taking only 55%–84% of the scheduled drugs or even less. Similar analysis of data in our OSAKO trial confirm this observation: a group of patients (N+ or N–) receiving more than 90% of LMF show a definite trend to a higher RFS rate at 5 years than those with less than 89% of LMF, the latter group demonstrating no difference in RFS from the untreated controls (Table 6), indicating that the dose problem seems to be highly critical.

Table 6. Relapse-free survival related to treatment intensity in adjuvant chemotherapy of breast cancer at 5 years

Group/study	Adjuvant regimen	Dose level (total dose)	RFS %	*P*
Milan (386 pts) [5]	CMF × 12	> 85%	79.3	0.04
	CMF × 12	84–55%	59.1	
	CMF × 12	< 55%	50.1	0.002
	Controls	–	48.2	
OSAKO St Gallen (241 pts) [19]	LMF × 6	> 90%	75.4	0.09
	LMF × 6	< 89%	59.0	0.01
	Controls	–	52.9	

Table 7. Results of palliative secondary treatment at first relapse after multimodal therapy

Group/ primary therapy	CR+PR %	Duration of response (months)	Survival with relapse (months)
Milan [40]			
Surgical controls	49	10	38
CMF × 12	41	10	30
St. Gallen/ OSAKO [45]			
Surgical controls	76 (53)	12 (11)	–
LMF × 6 + BCG	64 (36)	9 (10)	–

( ), Only patients with distant relapse

Pattern of First Relapse and Results of Subsequent Therapy

Several trials with 5 and more years of follow-up have now consistently shown that prolonged (6–24 months) adjuvant chemotherapy is able to alter the course of operable N+ breast cancer [6, 7]. It is interesting to note that this reduction in the number of relapses does not only apply to distant sites, but also results in a significantly reduced probability of *loco-regional* recurrences to a level of 6%–8%, which compares with that achieved by postoperative radiotherapy [7]. There is insufficient evidence as to whether adjuvant chemotherapy will change the pattern of first recurrences from that obtained with surgery alone: while preliminary data from Milan (CMF for 12 or 6 cycles) indicate a possible relative increase in relapse at hepatic or multiple organ sites our own analysis in the OSAKO trial showed no differences between patients treated by surgery alone or by additional LMF. Only the percentage of *pulmonary* metastases seems to be lower in both studies [19, 40].

There was some fear that patients pretreated with adjuvant chemotherapy would no longer respond favourably to *subsequent therapy* upon relapse. Results obtained in Milan after adjuvant CMF and in our group after LMF do not confirm this. The results of palliative secondary treatment at first relapse show comparable remission rates and remission duration as well as survival (once relapse has occurred) for surgical controls and previously treated women [39, 44]. It must be emphasized, however, that subsequent treatments were not prospectively standardized in either trial to settle this question with scientific precision (Table 7).

Patient Tolerance and Possible Late Toxicity of Adjuvant Chemotherapy

Table 8 summarizes the main characteristics of subjective and objective toxicity from adjuvant chemotherapy in breast cancer published in current trials. While treatment acceptance was excellent with L-PAM and oral LMF due to lack of significant gastrointestinal toxicity and alopecia, these problems definitely increased with prolonged treatment duration (SAKK trial, LMF 6 vs 24 cycles) or with increasing intensity of combination chemotherapy (CMF, CMFVP etc.), resulting in an increasing number of *patient drop-outs* during adjuvant therapy. Although the otherwise nearly universal alopecia with regimens containing adriamycin may be somewhat reduced by scalp hypothermia, this kind of adjuvant therapy poses additional problems of tolerance and psychological acceptance by younger patients. It is noteworthy that severe complications

Table 8. Patient tolerance of adjuvant chemotherapy regimen toxicity

Group	Regimen	GI	Alopecia	Drop-out	Drug death
NSABP	L-PAM	Good	None	?	0
	LF (M)	Moderate	Rare	?	2/> 300
OSAKO	LMF + BCG	Good	< 3%	2/118	2/118
SAKK	LMF6 or 24	Moderate (24)	Rare	24/400[b]	1/351
Milan	CMF 12	Moderate	55%	17/207	0
CALGB	CMF/CMFVP	Moderate	60%	?	2/499
Houston	FAC + BCG	Moderate	90%	?	1/222
Arizona	AC	Moderate	90%[a]	?	0
					8/> 2000 (0.4%)

[a] Reduced to 50% by scalp hypothermia
[b] Nearly all during 2nd year of RX (LMF × 24)

Table 9. Second neoplasms within > 5 years post mastectomy and adjuvant therapy in breast cancer

Group/regimen	No.	Patients with second tumors		(Acute) leukemias
		Opposite breast	Other site	
Milan [40]				
Surgical controls	179	4	3 (1.7%)	0
CMF × 12	207	3	2 (0.8%)	0
St. Gallen/OSAKO [44]				
Surgical controls	123	1	5 (4.0%)	2 AML
LMF × 6 + BCG	118	0	1 (0.8%)	0
NSABP/USA [26]				
Surgical controls	108	1	2 (1.8%)	0
L-PAM × 2 y	103	1	6 (5.8%)	1 AML
EFSCH/USA [32]				
Surgical controls	77	5	4 (5.2%)[a]	0
Thio TEPA × 1 y	90	2	4 (5.2%)[a]	1 CLL

[a] Including skin (basal cell) cancers

resulting in clear-cut *drug-induced death* were observed very infrequently: they have so far been reported in four of seven studies involving more than 2,000 patients with an overall frequency of 0.4% (*Table 8*).

There was (and still is) much theoretical debate concerning the possible risk of unpredictable late toxicity, especially the potential increase in *second tumours* after prolonged courses of adjuvant chemotherapy. Data for long-lasting immunosuppression are known from transplant recipients, from animal adjuvant chemotherapy trials with CMF or alkylating agents [15], and finally from combined intensive radiochemotherapy of Hodgkin's disease [15, 37]. However, present data after 5 and more years of median follow-up in controlled trials do *not* substantiate this fear for breast cancer adjuvant chemotherapy, at least not for the Milan trial with 1 year of intermittent CMF or for the OASKO trial with 6 months of intermittent LMF: in both studies the rate of second tumours (other than contralateral breast tumours) was 0.8% after 5 years and less than the 'natural rate' of second tumours after surgery alone (Table 9). I would like to draw attention to two cases of AML among the 123 patients of our surgical control arm, occurring after 2 and 4 years, respectively [44]. The increased incidence of either acute leukaemias or solid tumours of other sites has been known prior to the area of adjuvant chemotherapy in breast cancer [13, 38]. It is possible that long-term use of L-PAM or thio-TEPA (or prolonged use of other types of adjuvant regimens for over 6–12 months) will result in some slight increase in the second tumour rate, as suggested by the NSABP L-PAM trial (Table 9). This would constitute one more reason for using intensive combination cycles and shortening adjuvant treatment duration if possible.

Adjuvant Chemotherapy in Node-negative Patients?

Since several regimens of adjuvant chemotherapy have been shown to prolong RFS and possibly OAS in N+ patients, it seems logical to apply this approach to N− women with lesser residual tumour burden after mastectomy, in an effort to obtain cures [45]. Only limited data on this topic are available at present. An earlier study by Kardinal and Donegan [32] with thio-TEPA resulted in a long-term increase of RFS and OAS up to 10 years in N− patients, and our own trial with LMF + BCG in Eastern Switzerland still shows significantly increased RFS and especially OAS after 5 years of median follow-up in N− patients [44]. However, adjuvant chemotherapy in this risk group has to be considered still highly

Table 10. Results of controlled breast cancer trials with adjuvant hormonotherapy (5-year results) in N+ patients

Group	No.	Treatment	Essential findings	
			% RFS	% OAS
1. Historical studies				
NSBAP	43	RM	27 (− 3%)	40 (− 1)
	78	RM + Oophorectomy	24	39
Manchester	200	RM vs	39 (+ 10%)	48 (+ 8)
	203	RM + ovarian RT	49	56
Canada-UK < 45 years	58	RM vs	40 (+ 11%)	46 (+ 15)
	61	RM + ovarian RT	51	61
⩾ 45 years	44	RM vs	48	59
	47	RM + ovarian RT	60 (+ 12%)	64 (+ 5%)
	52	RM + ovarian RT + Pred	69 (+ 21%)	77 (+ 18%)
Oslo	193	RM + castration (surgery or RT)	60[a]	70[a]

Data from Bonadonna and Valagussa [6]
[a] No surgical controls

experimental, but probably as rewarding as the trials in N+ patients, since 25%–35% of these so-called good-risk patients are finally going to die from their tumour recurrence within 10 years after mastectomy [25, 50]. Several studies arising from our pilot data are now in progress to (1) single out valid risk factors such as oestrogen receptor positivity, intramammary lymphangiosis, or vascular invasion to select N− patients at higher risk of relapse; and (2) confirm in a controlled fashion and in large populations the potential value of short, but intensive courses of adjuvant chemotherapy [2, 33; ECOG trial started in 1981]. It will take at least 5 more years to settle this question for practical routine use.

Adjuvant Endocrine Therapy: Unexpected Revival

Historical trials conduced in recent decades and involving radical mastectomy with additional castration (surgical or by radiation) in premenopausal women have usually yielded no, or at best marginal, benefit as judged by RFS and OAS at 5 and more years (Table 10). However, a Canadian-British trial [34] of ovarian radiation plus long-term low-dose prednisone resulted in a significant increase of RFS and OAS in perimenopausal women over 45 years. The availability of *hormone receptor* data from primary brest tumours and the advent of low-toxicity endocrine treatment of breast cancer metastases with *anti-oestrogens* (tamoxifen), coupled with some frustration about the 'only partial success' and the subjective toxicity of adjuvant chemotherapy, stimulated a recent resurgence of adjuvant hormonotherapy trials in operable breast cancer (Table 11). Usually tamoxifen together with some type of combination chemotherapy is compared randomly with the same chemotherapy alone, but there are also studies which test the use on anti-oestrogens vs surgical controls, especially in postmenopausal women. Since all these studies are still of less than 3 years' median observation time, it seems too early to draw any firm conclusions, although recently published findings by NSABP investigators indicate some early increased RFS at 2 years with tamoxifen in addition to L-PAM + fluorouracil for a selected subset of postmenopausal ER+ women [27]. Several trials with more than 2000 patients are currently in progress; their results should be awaited before adjuvant endocrine therapy is given routinely to possibly unsuitable groups of patients.

Present Indications and Future Problems

It is difficult to advise the medical public now about the final merits and specific indications for adjuvant (chemo)therapy in breast cancer [6, 26]. It seems to work somehow, at least in N+ patients, but we still do not know how to use it best or which patients to give it to, to prevent either under- or overtreatment. The whole problem has become an enormous semi-scientific arena in which clinical investigators are under pressure from all sides: patients demanding treatment, politicians, community, research funders, health insurance administrators, and mass media, an unholy situation beautifully illustrated by Fisher in one of his recent publications [22]. However, I would

Table 11. Study design and preliminary results of adjuvant current (chemo)-hormonotherapy in operable breast cancer

Group	Adjuvant treatment	Essential findings
NSABP[a] [27]	PAM + FU vs PAM + FU + TAM	↗ RFS at 2 years in post-m. ER + pts
SWOG[b]	TAM vs CMFVP vs CMFVP + TAM	Too early
ECOB[b]	RM vs RM + TAM	Too early
Ludwig/[a] SAKK [33]	CMFP vs CMFP + oophorectomy	Pre-m. ⩾ 4, pos. LN to early
	TAM + prednisone RM	Post-m. > 70, y. to early
	RM TAM + prednisone CMFP + TAM	Post-m. < 70, y. to early

Data partly from Weiss et al. [55]
[a] All age groups + regardless of (determined) ER values
[b] Only ER +

Table 12. Adjuvant therapy of operable breast cancer: Are there standard indications in 1982?

N+ Patients:	Adjuvant CT generally *prolongs RFS* up to 5–6 years postop., probably depending on menopausal age. Prolongation of OAS = marginal in some studies		
1–3 nodes:	CMF × 6–12		
⩾ 4 nodes:	'More intensive'?	CMF × 6–12 AC or FAC CMFVP	[+ Tamoxifen or oophorectomy in ER + patients?]
N− Patients:	Adjuvant CT (or HT) still *experimental,* but seems to *work* Selection of potential 'high-risk groups' (ER−, tumor size, IML, IVI, etc.)		

RFS, relapse-free survival; OAS, overall survival; CT, chemotherapy; HT, hormonotherapy; IML, intramammary lymphangiosis; IVI, intramammary blood vessel invasion; ER, estrogen receptor

like to urge any responsible oncologist to stick to presently known facts rather than to yield to uncontrolled or even commercially motivated use of adjuvant treatments.

Preliminary indications (Table 12) in operable patients include the judicious use of one of the established adjuvant regimens, preferably six cycles of CMF, in patients with one to three positive nodes. Whether a shorter duration would be sufficient has to be investigated in scientific trials and not in private practice. Regarding the results of most trials other than the Milan and NSABP L-PAM studies, it seems it would be logical to give this treatment to pre- as well as postmenopausal women if they can be treated with adequate doses of CMF. L-PAM might be a substitute in this nodal group for some patients unwilling or unable to tolerate CMF, but seems to work only in premenopausal patients [26]. Clearly, *oral* LMF as used in the Swiss trials [31, 43] is no effective adjuvant chemotherapy for N+ women. Whether the high-risk patient group with four and more positive axillary nodes requires 'more intensive' adjuvant chemotherapy and will eventually benefit from this increased intensity of treatment remains to be demonstrated. Meanwhile, these patients may profit from the standard six or twelve cycles of CMF or other intensive regimens such as CMFVP, AC, or FAC. The addition of endocrine measures cannot be recommended as proven and should be reserved for clinical studies [6]. Clearly, adjuvant therapy of any kind in N− patients remains experimental and should not now be applied outside of well-controlled trials, even if there are indications that it would be of potential benefit [32, 43, 44]. There is no indication in my view for adjuvant radiotherapy after some type of radical mastectomy, nor does adjuvant immunotherapyet have any scientific basis for routine use.

Table 13. Present and future questions in adjuvant therapy of breast cancer: Prospective studies needed 1981

There is a need for prospective studies to evaluate:
1. N+ Patients (chemotherapy)
Treatment intensity? (different dose levels)
Treatment duration? (12 → 6 → 3 → 1 cycle)
Treatment onset? (post-, peri-, preop.)
Sequential adjuvant CT?
2. N− Patients
Adjuvant therapy necessary? (CT, HT, comb.)?
Treatment toxicity (acceptance)
3. Value of combinations or alternatives (N+ and N−)
Adjuvant CT ± endocrine measures ?
Adjuvant CT vs endocrine measures alone (ER+)?
Adjuvant CT ± "immunostimulants"?
Adjuvant CT ± radiotherapy? (esp. N ⩾ 4)
Limited surgery ± radiotherapy ± adj. CT?

For the first time in more than 40 years, long-term results of treatment for breast cancer are showing improvement, which is exciting both for the patients involved and for the whole medical community [6, 22]. Unfortunately, as Table 13 demonstrates, any scientific progress invariably generates more questions than answers during a certain evolutionary period. Current and future prospective trials are badly needed to clarify the problems of intensity, duration, and onset (post-, peri- or even preoperative?) of treatment. Can the effectiveness of adjuvant chemotherapy be increased by the use of sequential drug combinations [8] or by the addition of endocrine measures, immunostimulants, or radiotherapy in high-risk patients with more than four axillary nodes involved? Has adjuvant chemotherapy any place in N− patients and how does it fit in with the evolving concept of limited surgery and adjuvant radiotherapy in women with small primary tumors? How can treatment toxicity and acceptance be ameliorated?

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