Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis

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Background: **Interest in the use of preoperative systemic treatment in the management of breast cancer has increased because such neoadjuvant therapy appears to reduce the extent of local surgery required. We compared the clinical end points of patients with breast cancer treated preoperatively with systemic therapy (neoadjuvant therapy) and of those treated postoperatively with the same regimen (adjuvant therapy) in a meta-analysis of randomized trials.** ***Methods:*** **We evaluated nine randomized studies, including a total of 3946 patients with breast cancer, that compared neoadjuvant therapy with adjuvant therapy regardless of what additional surgery and/or radiation treatment was used. Fixed and random effects methods were used to combine data. Primary outcomes were death, disease progression, distant disease recurrence, and loco-regional disease recurrence. Secondary outcomes were local response and conservative local treatment. All statistical tests were two-sided.** ***Results:*** **We found no statistically or clinically significant difference between neoadjuvant therapy and adjuvant therapy arms associated with death (summary risk ratio [RR] = 1.00, 95% confidence interval [CI] = 0.90 to 1.12), disease progression (summary RR = 0.99, 95% CI = 0.91 to 1.07), or distant disease recurrence (summary RR = 0.94, 95% CI = 0.83 to 1.06). However, neoadjuvant therapy was statistically significantly associated with an increased risk of loco-regional disease recurrences (RR = 1.22, 95% CI = 1.04 to 1.43), compared with adjuvant therapy, especially in trials where more patients in the neoadjuvant, than the adjuvant, arm received radiation therapy without surgery (RR = 1.53, 95% CI = 1.11 to 2.10). Across trials, we observed heterogeneity in the rates of complete clinical response (range = 7%–65%;** ***P*** **for heterogeneity of <.001), pathologic response (range = 4%–29%;** ***P*** **for heterogeneity of <.001), and adoption of conservative local treatment (range = 28%–89% in neoadjuvant arms,** ***P*** **for heterogeneity of <.001).** ***Conclusions:*** **Neoadjuvant therapy was apparently equivalent to adjuvant therapy in terms of survival and overall disease progression. Neoadjuvant therapy, compared with adjuvant therapy, was associated with a statistically significant increased risk of loco-regional recurrence when radiotherapy without surgery was adopted.** **[J Natl Cancer Inst 2005;97:188–94]**

Non–metastatic breast cancer is increasingly accepted as a systemic disease rather than a local disease, and interest in the use of systemic preoperative therapy (neoadjuvant chemotherapy and endocrine therapy, also known as primary or induction therapy) to treat the early systemic aspects of the disease is, therefore, increasing *(1)*. Systemic neoadjuvant chemotherapy, moreover, may result in local tumor regression or even in a complete pathologic response. Neoadjuvant therapy may also reduce the extent of local surgery required from radical mastectomy to breast-conserving surgery (e.g., quadrantectomy, segmentectomy, or lumpectomy) without jeopardizing patient survival because the extent of local surgery in patients with breast cancer does not appear to influence major patient outcomes, such as survival and disease-free survival *(2–4)*.

Neoadjuvant therapy has been found to lead to better control of systemic residual disease in results from animal models *(5–7)*. Excision of primary tumors in mice leads to the release of serum growth-stimulating factors from the tumors and of malignant cells that can form metastatic foci *(6)*. When therapy with cyclophosphamide, radiation, tamoxifen, or luteinizing hormone-releasing hormone was preoperatively administrated to tumor-carrying mice, both tumor-cell proliferation and the release of growth-stimulating factors into the serum were suppressed, and survival was improved *(5,7)*. Thus, in mice, neoadjuvant therapy appears to be associated with better local and systemic disease control.

The same regimens administered as neoadjuvant therapy and adjuvant therapy (i.e., postoperative therapy) have been compared in randomized trials *(8–24)*. We used all available evidence from these trials to assess whether neoadjuvant systemic therapy is associated with any advantage compared with the same adjuvant systemic therapy for the treatment of breast cancer. The primary outcomes that we considered included loco-regional disease recurrence, distant disease recurrence, and overall survival; secondary outcomes included local response and the extent of breast surgery required. To address these issues, we performed a meta-analysis of randomized controlled trials that compared the same treatment regimen for breast cancer as neoadjuvant therapy and as adjuvant systemic therapy. We aimed to generate summary estimates, assess the remaining uncertainty, and estimate the between-study heterogeneity for each clinical outcome.

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Materials and Methods

Identification of Randomized Studies

We searched MEDLINE and EMBASE by entering the following in the searching algorithm: breast cancer AND (neoadjuvant OR neo-adjuvant OR pre-operative OR preoperative OR induction) AND (clinical trial OR randomized controlled trial OR double-blind OR single-blind OR random OR randomized OR placebo). We also searched the Cochrane Central Register of Controlled Trials for randomized trials that compared neoadjuvant with adjuvant systemic treatment for breast cancer. We set no language restriction. The latest search was done on October 31, 2003. We also hand-searched for the years 1995 through 2003 several oncology journals that publish many randomized trials *(25)* to ensure that electronic searches would not miss reports of eligible studies *(26)*. The reference list of retrieved papers was further screened for additional publications, and, to minimize publication bias, several investigators in the field were contacted and asked to provide clarifications and, potentially, additional data.

Eligibility Criteria

All randomized controlled studies that compared neoadjuvant with adjuvant systemic treatment (chemotherapy or endocrine therapy) for breast cancer, in which the same regimen was given preoperatively to one group and postoperatively to another group, were considered eligible regardless of what additional surgery or radiation treatment was used. We also accepted trials where one arm received exclusively postoperative therapy while the other arm received some cycles of the same regimen preoperatively and some other cycles postoperatively. We included trials regardless of the exact chemotherapeutic or endocrine regimens being used because results in animal models had shown that the beneficial effects of neoadjuvant chemotherapy and endocrine therapy appeared similar for both treatments *(5,7)*. In addition, all regimens try to reduce tumor burden either by killing cells or by blocking their hormonal stimulation and proliferation. The emphasis of the meta-analysis is on the timing of administration of the treatment, not on the specific types of drugs used or drug regimens.

We excluded meeting abstracts, escalation dose studies, and pseudorandomized trials (e.g., those with alternate allocation of subjects). If other concomitant anticancer nonsurgical treatments were also used (e.g., hormone therapy and radiation therapy), these treatments should not have differed systematically between the two arms. Whenever more than one publication reported results for the same group of patients, we included only the report with the longest follow-up (largest number of events) to avoid duplication of information. Data from interim analyses were included if no further final report was available.

Data Extraction and Outcomes

We recorded the following information about each eligible trial: authors' names, journal and year of publication, country of origin of patients, inclusive dates of patient enrollment, number of centers involved, and study design items (including whether there was a description of the mode of randomization, allocation concealment, number of withdrawals per arm, and blinding). We recorded the following information from both arms of each eligible trial: the number of patients randomly assigned to treatment and analyzed per arm, their age, their tumor stage, their menopausal status, regimens used (including type of therapy [endocrine therapy and/or chemotherapy], timing, number of courses for each arm, and additional treatments given to both arms), and number of outcome events per arm.

Primary outcomes included death (from any cause), disease progression, loco-regional disease recurrence, and distant disease recurrence (metastasis). Disease progression was defined as loco-regional or distant recurrence, occurrence of contralateral cancer, or death. Loco-regional recurrence was defined as recurrence in the ipsilateral breast or in the ipsilateral regional lymph nodes or chest wall.

Secondary outcomes included the local clinical response to neoadjuvant treatment (three categories: complete versus partial versus none or progressive disease), the pathologic response (complete versus noncomplete) in the neoadjuvant arm, and the surgical approaches adopted (no surgery needed [radiotherapy only], breast-conserving surgery [e.g., lumpectomy or quadrantectomy], or mastectomy) in each arm. After preoperative chemotherapy, the absence of clinical evidence of tumor in the breast was defined as a clinically complete response and a reduction in the clinical tumor size of 50% or more was defined as a partial response. A complete pathologic response was defined as the absence of tumor in the surgical specimen (primary tumor and lymph node metastasis); this response was pertinent only for women who had surgery after neoadjuvant treatment.

Two investigators (DM, JPAI) extracted the relevant data, and consensus was reached on all outcomes. Whenever information for outcomes was missing, we contacted the primary investigators to obtain additional data and clarifications.

Statistical Analysis

For all primary outcomes in each study, we estimated the risk ratio (RR), with its variance and 95% confidence interval (CI). In studies that did not provide explicit accounting of the numbers of events for each arm, we derived the pertinent numbers from the Kaplan-Meier curves presented, from other information available in the published reports, or from communication with primary investigators. For some outcomes in one study *(8),* we used hazard ratio estimates and 95% confidence intervals derived from proportional hazards modeling. Hazard ratios may be more appropriate than risk ratios for synthesizing data from time-to-event studies, but these ratios were rarely reported in adequate detail. Heterogeneity between the risk ratios for the same outcome between different studies was assessed by use of the chi-square-based Q statistic *(27)*. Data were then combined across studies by the use of general variance methods with fixed and random effects models *(27)*. The fixed effects analysis weighted the natural logarithm of each study's risk ratio by the inverse of its variance. The random effects analysis weighted the natural logarithm of each study's risk ratio by the inverse of its variance plus an estimate of the between-study variance in the presence of between-study heterogeneity. In the absence of between-study heterogeneity, fixed and random effects coincide because the between-study variance is zero. For the secondary outcomes, we estimated whether there was statistically significant between-study heterogeneity. When very large between-study heterogeneity was detected, we did not present weighted summary estimates.

Table 1. Characteristics of eligible trials for this meta-analysis*

Study (reference)	No. patients enrolled (analyzed)	Mean age (median), y		Stage* (size in cm)	% Menopausal	Regimens (No. of Nadj. arms/No. of all courses)†	Enrollment interval (yr)	Country (No of centers)	Median follow-up, mo
		Nadj.	Adj.						
Avril et al. *(9)*	272	53	53	T2-3 N0-1 (>3)	54	EVM, ETV (6/6)	1985–89	France (1)	124
Mauriac et al. *(10)*									
Semiglazov et al. *(11)*	271	50	51	IIB IIIA	No data	TMF (1–2/6)	1985–90	Russia (1)	53
Scholl et al. *(12)*	196 (181)	(49)	(51)	T2-3 N0-1b	37	FAC (2/6)	1983–86	France (1)	54
Scholl et al. *(13)*	414 (390)	45	45	T2-3 N0-1b1 *(3–7)*	0	FAC (4/4)	1986–90	France (1)	105
Broet et al. *(14)*									
Makris et al. *(15)*	309 (293)	(56)	(55)	T0-4 N0-1	61	MM(M)/TAM (4/8)	1990–95	United Kingdom (1)	48
NSABP B-18 *(16,17)*	1523 (1493)	50	50	T1-3 N0-1	49	AC (4/4)	1988–93	USA, Canada (32)	114‡
Gazet et al. *(18)*	210	52	53	T1-4 N0-2	63	Gsr, Frm, MMM (4/8)	1990–93	United Kingdom (1)	>60
van der Hage et al. *(8)*	698	≤50	≤50	$T1_c$–4_b N0-1	45	FEC (4/4)	1991–99	International (17)	56
Danforth et al. *(19)*	53	(49)	(43)	II	40	FLAC/G-CSF (5/5)	1990–95	USA (multiple)	108

*For specific definitions of the staging system used, see the respective reference(s). Nadj. = neoadjuvant; Adj. = adjuvant; EVM = epirubicin, vincristine, and methotrexate; ETV = mitomycin, thiothepa, and vindesine; TMF = thiotepa, methotrexate, and fluorouracil ; FAC = fluorouracil, doxorubicin, and cyclophosphamide; AC = doxorubicin and cyclophosphamide; TAM = tamoxifen ; NSABP = National Surgical Adjuvant Breast and Bowel; MMM = mitoxantrone, mitomycin, and methotrexate; Gsr = goserelin; Frm = formestane; FEC = fluorouracil, epirubicin, and cyclophosphamide; FLAC/G-CSF = fluorouracil, leucovorin, doxorubicin, cyclophosphamide, and granulocyte colony-stimulating factor support.

†The number of neoadjuvant courses refers to the number of courses given preoperatively in the neoadjuvant arm. The number of all courses refers to the total number of chemotherapy courses; this was the same in both the neoadjuvant and adjuvant arms.

‡Mean.

We also performed subgroup analyses for the primary outcomes on the basis of whether conservative local management (e.g., lumpectomy or quadrantectomy) or radiotherapy only, without surgery, was used more often in the neoadjuvant arm than in the adjuvant arm.

Finally, for the primary outcomes, we evaluated whether small and large studies might have yielded different results from each other [by use of the Begg-Mazumdar test based on Kendal's tau correlation coefficient *(28)*] and whether the summary effect size changed considerably over time as more data accumulated [by use of recursive cumulative meta-analysis *(29,30)* and evaluation of Kaplan-Meier plots from individual studies for proportionality of hazards]. Analyses were conducted in Meta-Analyst (Joseph Lau, Boston, MA) and SPSS version 11.0 (SPSS, Inc., Chicago, IL). All statistical tests were two-tailed.

Results

Eligible Studies

We identified 12 potentially eligible studies *(8–24)* of neoadjuvant versus adjuvant therapy for patients with breast cancer. One study was excluded from the meta-analysis because no peer-reviewed report has been published, although it has been discussed briefly in review articles *(20–22)*. Two more trials *(23,24)* are ongoing, and no peer-reviewed report has been appeared for either.

Nine trials were thus eligible, as shown in Table 1 *(8–19)*. A total of 3946 patients were randomly assigned to treatment (1972 in neoadjuvant arms and 1974 in adjuvant arms), and we analyzed data from 3861 of them in this study (1933 and 1928 in the two arms, respectively). In four trials *(12–17),* a total of 85 patients did not have analyzable data. The mean or median age ranged between 43 years and 56 years across the arms of the included trials. There was considerable variability across studies in the eligible stages of breast cancer, tumor size, and lymph node status (Table 1). With the exception of one trial *(13)* that included only premenopausal patients, all trials included both premenopausal and postmenopausal patients. Many regimens were used (Table 1). The total number of treatment courses in the adjuvant treatment arms varied between four and eight, but the neoadjuvant courses varied between one and six. In four trials *(11,12,15,18),* patients in the neoadjuvant arm received some of the courses before surgery and some after surgery. In the other five trials, patients in the neoadjuvant arm received all courses before surgery. All nine trials enrolled patients between January 1983 and May 1999. Three of the nine trials were multicentric trials *(8,16,19)*.

Only one trial *(11)* described in detail the mode of randomization, and three trials *(8,18,19)* described the mode of allocation concealment in detail. Withdrawals were described in detail in seven trials *(8,9,12–17,19)*. None of the nine studies was blinded. The definition of loco-regional recurrence was similar across studies. However, three studies *(15,18,19)* did not provide detailed definitions for this outcome but simply separated it from systemic, distant, or metastatic recurrence or relapse without further specification. Complete pathologic response (no invasive tumor cells) was defined similarly in all studies in which it was analyzed *(8,11,15,16,17,19)*.

Meta-Analysis: Primary Outcomes

In the meta-analysis, we included data on 966 deaths from all nine trials *(8–19)*, on 1310 occurrences of disease progression from seven trials *(8–11,13–17, 19),* on 520 loco-regional recurrences from all nine trials *(8–19),* and on 745 distant recurrences from seven trials *(9–11,13–19)*. Although we contacted the authors, additional data could not be retrieved on disease progression from two trials *(12,18)* and on distant recurrences from two trials *(8,12)*.

We first used a fixed effects analysis to investigate differences between the compared arms for the outcomes death, disease progression, distant recurrences, and loco-regional recurrences. We

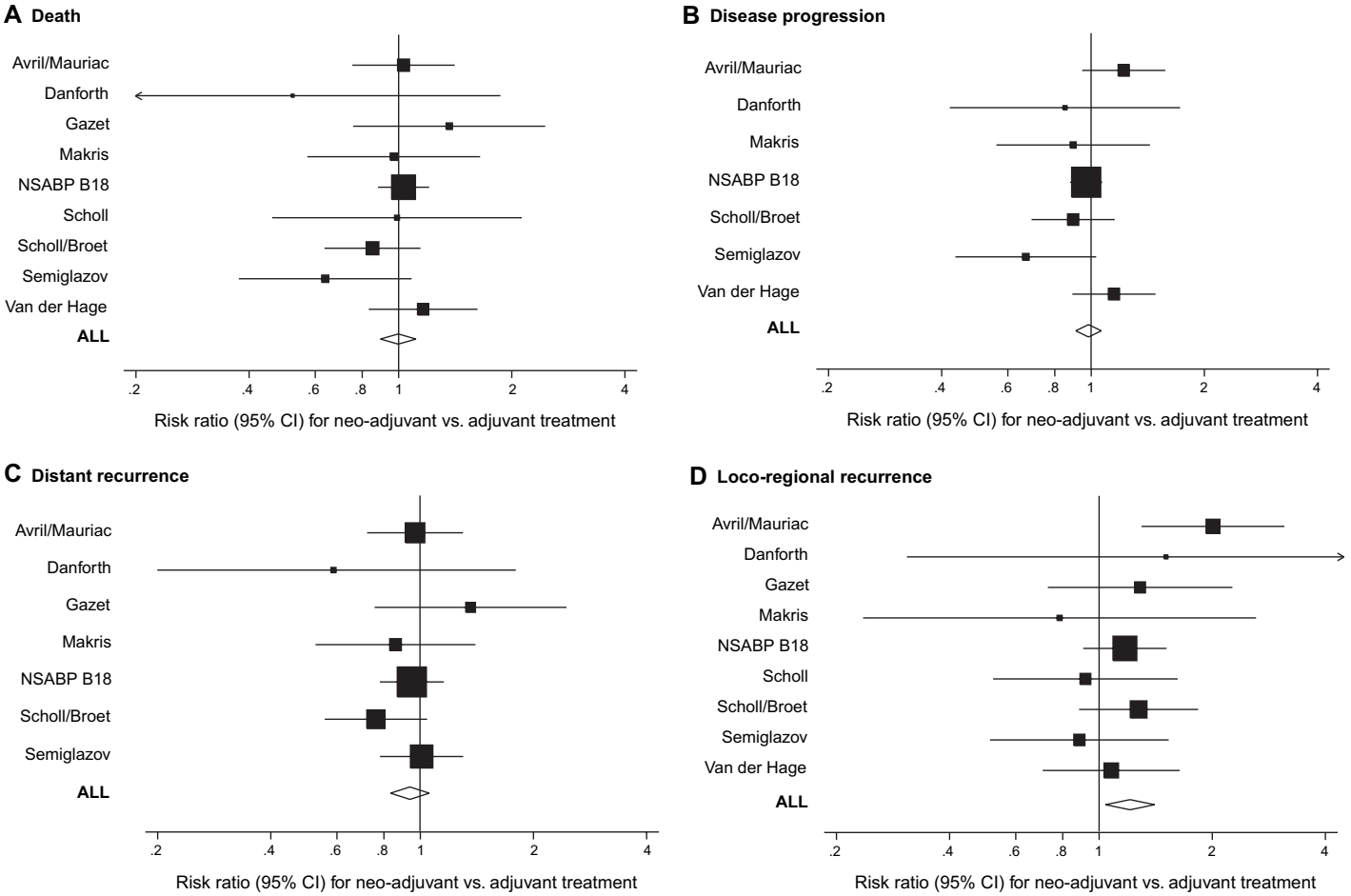

Fig. 1. Meta-analysis for primary outcomes with neoadjuvant therapy compared with adjuvant therapy for breast cancer. In each panel, each study [Van der Hage et al. *(8)*, Avril et al./Mauriac et al. *(9,10)*, Semiglazov et al. *(11)*, Scholl et al. *(12)*, Scholl et al. *(13)*, Broet et al. *(14)*, Makris et al. *(15)*, NSABP B-18 *(16,17)*, Gazet et al. *(18)*, Danforth et al. *(19)*] is shown by the point estimate of the risk ratio (square proportional to the weight of each study) and 95% confidence interval (CI) for the risk ratio (extending lines); the summary risk ratio (ALL) and 95% confidence intervals by fixed effects calculations are also shown by diamonds. For all panels, values greater than 1 indicate that neoadjuvant treatment has a worse outcome compared with adjuvant treatment. (A) Death. (B) Disease progression. (C) Distant disease recurrence. (D) Loco-regional disease recurrence. Arrow = 95% confidence interval extends beyond the depicted range.

found no difference between the arms for the outcomes death (summary RR for death = 1.00, 95% CI = 0.90 to 1.12), disease progression (summary RR for disease progression = 0.99, 95% CI = 0.91 to 1.07), and distant recurrences (summary RR for distant recurrence = 0.94, 95% CI = 0.83 to 1.06). However, we did find a statistically significant 22% increased relative risk for loco-regional recurrences associated with neoadjuvant treatment (summary RR for loco-regional recurrence = 1.22, 95% CI = 1.04 to 1.43; P = .015) (Fig. 1). No statistically significant between-study heterogeneity was observed for any of the four primary outcomes.

With a random effects analysis, we found no difference between arms compared for death and distant recurrences; in fact, the results calculated from the random effects analysis were identical to those obtained by fixed effects analysis (between-study variance = 0). Furthermore, the results for disease progression (summary RR = 0.99, 95% CI = 0.88 to 1.11) and loco-regional recurrence (summary RR = 1.22, 95% CI = 1.03 to 1.44; P = .018) were very similar to the results for the same outcomes from the fixed effects analysis. The difference in the results for loco-regional recurrences in the neoadjuvant treatment arms was less than 5% in seven trials *(8,11,12,15–19),* 16.1% in Avril et al. *(9),* and 5.6% in Broet et al. *(14)*.

Secondary Outcomes

Secondary outcomes are shown in Table 2. The rates of complete clinical response were statistically significantly heterogeneous (ranging from 7% to 65%, P for heterogeneity of <.001) across studies. When both complete and partial clinical responses were considered, the difference between extremes was smaller, but the rates were still statistically significantly heterogeneous (ranging from 45% to 83%, P for heterogeneity of <.001). Rates of pathologic response were available in five trials *(8,11,15–17, 19)* and were generally low but were still statistically significantly heterogeneous between studies (ranging from 4% to 29%, P for heterogeneity of <.001). In the other four trials *(9,10,12–14,18),* pathologic response rates were not available because radiotherapy was administered to patients who had a complete clinical response. Although the rates of pathologic response were not reported, these rates, by definition, would have been lower than the rates of complete clinical response. Thus, the rates of pathologic response in these four trials should not have exceeded the rates observed in the other trials and should have been lower than those.

We found large heterogeneity across studies in the rates of conservative local treatment in the adjuvant arms (ranging from

Table 2. Clinical and pathologic response rates of the studies in this meta-analysis in the neoadjuvant arm and local treatment adopted in each arm*

Study (reference)	Clinical response		% pathologic response	Local treatment adopted for breast cancer					
				No. of neoadjuvant treatment arms			No. of adjuvant treatment arms		
	% Complete	% Partial		RT	BSS	M	RT	BSS	M
Avril et al. *(9)*	33	30	U	44	40	49	—	—	138
Mauriac et al. *(10)*									
Semiglazov et al. *(11)*	12†	57†	29†	—	38	99	—	11	123
Scholl et al. *(12)*	13‡	32‡	U	41	32	22	29	26	31
Scholl et al. *(13)*	24	42	U	102	62	36	87	60	43
Broet et al. *(14)*									
Makris et al. *(15)*	22	61	7	1	132	16	2	111	31
NSABP B-18 *(16,17)*	36	43	13	—	504	239	—	450	302
Gazet et al. *(18)*	25	26	U	16	73	11	4	97	9
Van der Hage et al. *(8)*	7	42	4	—	120§	203§	—	79§	262§
Danforth et al. *(19)*	65‖	12‖	20‖	—	11	15	—	11	16

*RT = radiotherapy only; BSS = breast-sparing surgery; M = mastectomy; U = unknown rate of pathological response (patients with complete clinical response underwent radiotherapy without any surgery).

†Response rates related to neoadjuvant chemotherapy plus preoperative radiotherapy.

‡Data refer to only to 76 patients (subgroup 1a of the trial).

§In this trial, 698 patients were randomly assigned to treatment, but because 34 patients did not receive the surgical treatment stipulated by the study protocol (20 in the preoperative group and 14 in the postoperative group), only 664 patients underwent surgery and are included here.

‖Data refer only to 17 patients because tumor was completely removed during excisional biopsy in nine individuals.

0% to 92%; P for heterogeneity of <.001) and in the neoadjuvant arms (ranging from 28% to 89%; P for heterogeneity of <.001). Overall, we found a statistically significant higher rate of conservative local treatment in the neoadjuvant arms than in the adjuvant arms of five studies *(8,9–11,15–17)*, a borderline difference in another trial (P = .06) *(12),* and no difference between arms in three studies *(13,18,19)*. Finally, we found that radiotherapy only, without surgery, was administered statistically significantly more often in the neoadjuvant arms than in the adjuvant arms in three trials *(9,10,13,18)*.

We found no differences in the primary outcomes between the two arms in the subgroup of studies in which there was an excess rate of conservative local treatment in the neoadjuvant arms (e.g., for loco-regional recurrence, RR by random effects = 1.18, 95% CI = 0.91 to 1.52; P = .22; and RR by fixed effects = 1.19, 95% CI = 0.99 to 1.43; P = .063; no statistically significant between-study heterogeneity) and the subgroup of studies without such an excess in the former subgroup (e.g., for loco-regional recurrence, RR by both fixed and random effects = 1.31, 95% CI = 0.95 to 1.81; P = .097). However, increased risk of loco-regional recurrence associated with neoadjuvant treatment was driven largely by the three trials *(9,10,13,18)* in which radiotherapy only without surgery was adopted more often in the neoadjuvant than in the adjuvant arms (RR by random effects = 1.53, 95% CI = 1.11 to 2.10; P = .009; and RR by fixed effects = 1.53, 95% CI = 1.17 to 2.00; P =.002; no statistically significant between-study heterogeneity), whereas no association with loco-regional recurrences was found in other trials (RR by both fixed and random effects = 1.10, 95% CI = 0.87 to 1.38; P = .44). The strongest association between neoadjuvant treatment and increased risk of loco-regional recurrence was observed in the study in which the patients in the neoadjuvant arm with a complete clinical response received radiotherapy alone without any surgical treatment *(9,10)*. Patients who were treated only with radiotherapy had statistically significantly higher rates of loco-regional recurrence (20 of 44 patients) than patients who were treated with breast-conserving surgery (nine of 40 patients). Subgroup analyses should be interpreted cautiously because of multiple comparisons.

Potential Bias

Small trials did not differ from larger trials in their results for death (P =.46), distant disease recurrence (P = .45), or loco-regional recurrence (P = .84). However, there was an indication that smaller studies, compared with larger studies, had a relatively more favorable comparative overall disease progression associated with neoadjuvant treatment (P = .068) than with adjuvant treatment. The first study *(12)* did not show different results for any outcome than later studies *(8–11,13,19),* and the summary estimates did not change much as more data accumulated over time (data not shown).

Discussion

We found no difference in overall survival, disease progression, and distant disease recurrence between the neoadjuvant treatment arms and the adjuvant treatment arms in a meta-analysis of nine trials with a total of approximately 4000 subjects. Moreover, the cumulative data excluded modest even differences in these outcomes. However, neoadjuvant treatment compared with adjuvant treatment was statistically significantly associated with an increased risk of loco-regional disease recurrence, and the difference was greater in trials in which radiotherapy without any surgery was adopted more commonly in the neoadjuvant arm than in the adjuvant arm. Pathologic response rates were rather low regardless of the regimen used, and rates of conservative local management varied considerably across studies.

Primary systemic treatment has been accepted as the standard of care in women with locally advanced breast cancer *(31)*. Downstaging (i.e., the possibility of breast-conserving surgery for locally advanced breast cancer and for lesions more than 3 cm in diameter) and good cosmetic results are considered important advantages of neoadjuvant treatment. The use of primary systemic treatment for smaller, earlier-stage tumors is less well accepted. No trial included in our meta-analysis had a difference in survival or disease progression between neoadjuvant arms and adjuvant arms. From the results of the largest trial *(16,17)* alone, we could

exclude differences of 20%–30% between the compared strategies by taking into account the uncertainty of the observed hazard ratios. In our meta-analysis, we excluded differences of 12% for mortality and differences of 9% for disease progression on the basis of the uncertainty of the observed summary risk ratios, thus narrowing the potential for differences of any importance between the two arms. Overall survival is not influenced by the timing of chemotherapy (before or after surgery) but is more likely to be influenced by the chemosensitivity of the primary lesion *(32–34)*. Thus, this meta-analysis did not confirm that neoadjuvant systemic therapy was associated with better clinical outcomes than adjuvant systemic therapy.

In fact, we found that a statistically significantly higher relative risk of loco-regional disease recurrence was associated with neoadjuvant treatment than with adjuvant treatment. We found no clear association between the risk of loco-regional recurrence and the use of breast-conserving surgery, although data from individuals are required to address this issue more appropriately. Large trials *(2,3)* have found a higher risk of loco-regional disease recurrence associated with breast-conserving surgery than with more extensive surgical approaches. We found, however, that the increased risk in the neoadjuvant arm largely reflected the use of radiotherapy without any surgery for patients who had an apparently complete clinical response. The loco-regional recurrence problem is compatible with the low rates of complete pathologic response that we observed in these trials. Similarly, low rates of pathologic response (<20%) have also been obtained in trials comparing various neoadjuvant regimens with each other *(35,36)*. The lack of pathologic response appears to be associated with an adverse outcome in the neoadjuvant arms *(16,37)*. Consequently, despite gross clinical response, the tumor bed may not be free of malignant cells, and tumor cell foci may be present in the majority of patients, increasing the risk for subsequent loco-regional disease recurrence. This problem is probably more important when radiotherapy alone is used. An alternative explanation may be that these women would have more breast tissue in which to develop a loco-regional recurrence.

Our meta-analysis has some limitations. We found some evidence that small trials gave different results from larger trials for disease progression, and publication bias cannot be totally excluded. We have to acknowledge that the meta-analysis is based on data from trials that have published results in the literature. Use of updated individual patient data may further enhance the accuracy and reduce the uncertainty of the estimates *(38,39)*. However, we made an effort to include all additional information that we could obtain from the primary investigators, and definitions for the major outcomes were largely consistent across studies. A meta-analysis of individual-level data may still be performed with an emphasis on identifying patients who have different risks for the major outcomes *(40)*. Another potential limitation is that the results of at least two recently launched randomized studies *(23,24)* with a total of 1315 patients were not available to include in the meta-analysis. However, given the accumulated evidence to-date, the overall summary estimates for the primary outcomes that we considered are unlikely to change.

Another limitation of this study is that there was considerable heterogeneity in the design, modes of treatment used in each study, and response rates. Heterogeneity is not necessarily a disadvantage in meta-analysis *(41)*, and in our study, it provided an opportunity to probe the consistency of the treatment effects across the various local treatment approaches used. In particular, there was large variability in the treatment regimens used across these studies, and a meta-analysis for specific regimens would not be feasible. We initially hypothesized, on the basis of results from animal studies and a commonly postulated mechanism, that the relative merits of neoadjuvant and adjuvant therapies do not differ by the regimen used. This potential limitation should be considered seriously. In the meta-analysis, we found no evidence of between-study heterogeneity for any primary outcome despite this variability in treatments. Thus, from the available data, we cannot reject the hypothesis that the specific treatment regimen does not influence the relative merits of neoadjuvant therapy compared with adjuvant therapy. It may be argued, however, that the effect sizes from this meta-analysis should not be extrapolated necessarily to agents with much higher potency or very different modes of action. For example, some recent studies suggest that regimens involving taxanes and/or the monoclonal antibody trastuzumab may be particularly effective as neoadjuvant regimens *(42–44)*. However, none of these regimens have been evaluated in randomized trials that compared neodjuvant therapy with adjuvant therapy.

Despite these caveats, this meta-analysis demonstrates the equivalence of neoadjuvant and adjuvant treatments for breast cancer in terms of survival, disease progression, and distant recurrence and shows that an increased risk of loco-regional disease recurrence is associated with neoadjuvant treatment, especially when primary systemic treatment is not accompanied by any surgical intervention (i.e., radiation therapy alone). Consequently, we recommend avoiding the use of radiotherapy without any surgical treatment, even in the presence of an apparently good clinical response to neoadjuvant chemotherapy. Some sort of breast-conserving surgical intervention is likely to be warranted, regardless of whether neoadjuvant or adjuvant treatment is adopted and regardless of the patient's initial clinical response.

References

(1) Buchholz TA, Hunt KK, Whitman GJ, Sahin AA, Hortobagyi GN. Neoadjuvant chemotherapy for breast carcinoma: multidisciplinary considerations of benefits and risks. Cancer 2003;98:1150–60.

(2) Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–32.

(3) Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.

(4) Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N, et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 2002;347:567–75.

(5) Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. Cancer Res 1983;43:1488–92.

(6) Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. Cancer Res 1989;49:1996–2001.

(7) Fisher B, Saffer E, Rudock C, Coyle J, Gunduz N. Effect of local or systemic treatment prior to primary tumor removal on the production and response to a serum growth-stimulating factor in mice. Cancer Res 1989;49:2002–4.

(8) van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224–37.

(9) Avril A, Faucher A, Bussieres E, Stockle E, Durand M, Mauriac L, et al. Results of 10 years of a randomized trial of neoadjuvant chemotherapy in breast cancers larger than 3 cm. Chirurgie 1998;123:247–56. [In French.]
(10) Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M, et al. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. Institut Bergonie Bordeaux Groupe Sein (IBBGS). Ann Oncol 1999; 10: 47–52.
(11) Semiglazov VF, Topuzov EE, Bavli JL, Moiseyenko VM, Ivanova OA, Seleznev IK, et al. Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer. Ann Oncol 1994;5:591–5.
(12) Scholl SM, Asselain B, Palangie T, Dorval T, Jouve M, Garcia Giralt E, et al. Neoadjuvant chemotherapy in operable breast cancer. Eur J Cancer 1991;27:1668–71.
(13) Scholl SM, Fourquet A, Asselain B, Pierga JY, Vilcoq JR, Durand JC, et al. Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery: preliminary results of a randomised trial: S6. Eur J Cancer 1994;30A:645–52.
(14) Broet P, Scholl SM, de la Rochefordiere A, Fourquet A, Moreau T, De Rycke Y, et al. Short and long-term effects on survival in breast cancer patients treated by primary chemotherapy: an updated analysis of a randomized trial. Breast Cancer Res Treat 1999;58:151–6.
(15) Makris A, Powles TJ, Ashley SE, Chang J, Hickish T, Tidy VA, et al. A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. Ann Oncol 1998;9:1179–84.
(16) Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672–85.
(17) Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001;30:96–102.
(18) Gazet JC, Ford HT, Gray R, McConkey C, Sutcliffe R, Quilliam J, et al. Estrogen-receptor-directed neoadjuvant therapy for breast cancer: results of a randomised trial using formestane and methotrexate, mitozantrone and mitomycin C (MMM) chemotherapy. Ann Oncol 2001;12:685–91.
(19) Danforth DN Jr, Cowan K, Altemus R, Merino M, Chow C, Berman A, et al. Preoperative FLAC/granulocyte-colony-stimulating factor chemotherapy for stage II breast cancer: a prospective randomized trial. Ann Surg Oncol 2003;10:635–44.
(20) Ragaz J. Emerging modalities for adjuvant therapy of breast cancer: neoadjuvant chemotherapy. NCI Monogr 1986;1:145–52.
(21) Ragaz J. Preoperative (neoadjuvant) chemotherapy for breast cancer: outline of the British Columbia Trial. Recent Results Cancer Res 1986;103:85–94.
(22) Ragaz J, Baird R, Rebbeck P, Coldman A, Goldie J. Neoadjuvant-preoperative-chemotherapy for breast cancer—preliminary report of the Vancouver trial. Prog Clin Biol Res 1985;201:77–87.
(23) Jakesz R, for ABCSG. Comparison of pre- vs. postoperative chemotherapy in breast cancer patients: Four-years results of Austrian Breast & Colorectal Cancer Study Group (ABCSG) Trial 7. Proc Am Soc Clin Oncol 2001;20:125.
(24) Gianni L, Baselga J, Eiermann W, Porta VG, Semiglazov V, Garcia-Conde J, et al. First report of the European Cooperative Trial in Operable Breast Cancer (ECTO): Effects of primary systemic therapy (PST) on loco-regional disease. Proc Am Soc Clin Oncol 2002;21:34a.
(25) Grossi F, Belvedere O, Rosso R: Geography of clinical cancer research publications from 1995 to 1999. Eur J Cancer 2003;39:106–11.
(26) Hopewell S, Clarke M, Lusher A, Lefebvre C, Westby M. A comparison of handsearching versus MEDLINE searching to identify reports of randomized controlled trials. Stat Med 2002;21:1625–34.
(27) Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–6.
(28) Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
(29) Ioannidis JP, Contopoulos-Ioannidis DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. J Clin Epidemiol 1999;52:281–91.
(30) Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. Proc Natl Acad Sci USA 2001;98:831–6.
(31) Kaufmann M, von Minckwitz G, Smith R, Valero V, Gianni L, Eiermann W, et al. International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. J Clin Oncol 2003;21:2600–8.
(32) Aas T, Geisler S, Eide GE, Haugen DF, Varhaug JE, Bassoe AM, et al. Predictive value of tumour cell proliferation in locally advanced breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 2003;39:438–46.
(33) Ellis PA, Smith IE, McCarthy K, Detre S, Salter J, Dowsett M. Preoperative chemotherapy induces apoptosis in early breast cancer. Lancet 1997;349:849.
(34) Shao ZM, Li J, Wu J, Han QX, Shen ZZ, Fontana JA, Barsky SH. Neoadjuvant chemotherapy for operable breast cancer induces apoptosis. Breast Cancer Res Treat 1999;53:263–9.
(35) von Minckwitz G, Raab G, Shutte M, Hilfrich J, Blohmer JU, Gerber B, et al. Dose-dense versus sequential Adriamycin/docetaxel combination as preoperative chemotheraphy (pCHT) in operable breast cancer (T2–3 N0–2 M0): Primary endpoint analysis of the GEPARDUO study. Proc Am Soc Clin Oncol 2002;21:43a.
(36) NSABP: The effect on primary tumor response of adding sequential taxotere to adriamycin and cyclophosphamide: preliminary results of the NSABP protocol B-27. Breast Canc Res Treat 2001;69:210.
(37) Pierga JY, Mouret E, Dieras V, Laurence V, Beuzeboc P, Dorval T, et al. Prognostic value of persistent node involvement after neoadjuvant chemotherapy in patients with operable breast cancer. Br J Cancer 2000;83:1480–7.
(38) Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002;25:76–97.
(39) Clarke M, Stewart L, Pignon JP, Bijnens L. Individual patient data meta-analysis in cancer. Br J Cancer 1998;77:2036–44.
(40) Trikalinos TA, Ioannidis JP. Predictive modeling and heterogeneity of baseline risk in meta-analysis of individual patient data. J Clin Epidemiol 2001;54:245–52.
(41) Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. Lancet 1998;351:123–7.
(42) Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002;20:1456–66.
(43) Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003;21:4165–74.
(44) Buzdar AU, Hunt K, Smith T, Francis D, Ewer D, Booser E, et al. Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P) and antracycline-containing chemotherapy (CT): initial results of a randomised trial in operable breast cancer (BC) with HER/2 positive disease. New Orleans, LA: Proc ASCO, 2004 June 5–8. Proc Am Soc Clin Oncol 2004;23:7.

Notes

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