Overview of Randomized Perioperative Polychemotherapy Trials in Women With Early-Stage Breast Cancer

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Purpose: **To determine whether perioperative polychemotherapy (PeCT) can significantly prolong the overall survival of women with early-stage breast cancer.**

Methods: **A meta-analysis that used updated individual patient data from all available randomized trials of PeCT, both published and unpublished, was conducted. Data on 6,093 patients (1,124 deaths and 1,912 recurrences) from five clinical trials were available (median follow-up duration, 5.3 years; maximum, 11.3 years).**

Results: **No significant effect of PeCT on overall survival was observed. However, patients who received PeCT had a significantly longer disease-free survival (hazards ratio [HR], 0.89; 95% confidence interval [CI], 0.82 to 0.98; $P = .02$). Time to local recurrence was significantly prolonged in the PeCT arm (HR, 0.68; 95% CI, 0.58 to 0.80; $P < .0001$). Likewise, there was a borderline significant difference in favor of PeCT in terms of time to distant metastases (HR, 0.90; 95% CI, 0.81 to 1.00; $P = .05$). Subgroup analyses suggest that node-negative women benefited the most from treatment.**

Conclusion: **At present, there is no evidence that PeCT is able to prolong overall survival in patients with early-stage breast cancer; however, further follow-up evaluation is required. PeCT significantly prolongs disease-free survival, especially in node-negative women, which emphasizes once more the need for clinical trials in this subgroup.**

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ADJUVANT SYSTEMIC long-term polychemotherapy has been shown to prolong overall and disease-free survival of women with early-stage breast cancer.[1] An overview of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that adjuvant polychemotherapy resulted in a 28% decrease in the annual rate of recurrence and a 16% decrease in the annual rate of death.[1] Other important conclusions on the value of adjuvant chemotherapy were that long-term polychemotherapy (eg, 12 months) was not superior to shorter regimens (eg, 6 months). On the other hand, polychemotherapy appeared to be better than single-agent chemotherapy. Comparisons between trials that involved prolonged polychemotherapy, those that involved only preoperative or perioperative chemotherapy, and those that involved prolonged monotherapy indicated a significant heterogeneity of treatment effect for disease-free and overall survival ($P < .001$ for disease-free survival and $P < .05$ for overall survival), with the greatest therapeutic effect associated with prolonged polychemotherapy.[1] Consequently, the analyses presented in the EBCTCG overview were restricted to trials that assessed prolonged polychemotherapy and no results of trials that compared perioperative chemotherapy versus no perioperative chemotherapy were presented.

Perioperative polychemotherapy (PeCT) is defined as a short course of polychemotherapy that starts within 3 days after the patient has undergone surgery. Since the results of the first trial that used perioperative monochemotherapy were published by the National Surgical Adjuvant Breast and Bowel Project (NSABP),[2] many other collaborative groups have also studied whether starting chemotherapy perioperatively might change the course of early-stage breast cancer.[3-11] The majority of these trials have shown a significant advantage for perioperative chemotherapy, mainly in terms of disease-free survival, but not for overall survival. In view of these data, it was decided to conduct an overview of all known trials of PeCT to answer the question of whether there is a place for this therapy in the treatment of patients with early-stage breast cancer.

METHODS

Eligibility Criteria

Trials were eligible for inclusion in this overview only if they had randomized early-stage breast cancer patients between potentially

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curative surgery followed by PeCT and surgery without PeCT, where PeCT was defined as any polychemotherapy regimen that started within 3 days after the patient had undergone surgery. Additional adjuvant systemic therapy (ie, either prolonged chemotherapy or hormonal therapy or both) was allowed only if it was clearly specified in the trial protocol and was systematically given in all randomized treatment arms.

Data Collection

Every effort was made to include all existing randomized trials that involved PeCT in patients with early-stage breast cancer. To avoid publication bias, both published and unpublished studies were included. Published studies were identified by means of a computerized bibliographic search using the Medline Express system. Unpublished studies were found by hand-searching meeting abstracts of the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the European Cancer Conference (ECCO). Moreover, various experts in the field were also asked to identify studies that were possibly eligible for this overview. The cutoff date for the receipt of data for this overview was February 1994.

Data for all randomized patients, including those ineligible, lost, or withdrawn, were included. For all patients, baseline data on the following parameters were collected on the date of randomization: treatment allocated (including additional adjuvant treatments), age, menopausal status, surgical treatment, and axillary nodal status. Furthermore, updated follow-up information was collected on second primary tumors (including contralateral breast cancers), local recurrences, distant metastases, survival, and causes of death (the data form used in the EBCTCG overview was adopted with minor modifications). Definition of menopausal status was left to the discretion of the individual trial coordinators. In cases in which menopausal status was unknown, it was taken to be premenopausal in women known to be younger than 50, and postmenopausal otherwise. Forty cases with an unknown axillary nodal status were grouped together with those that had positive nodes. Extensive cross-checks of the data set were performed and, in case of any inconsistencies, the trial coordinator was contacted and the information was corrected if necessary.

Description of the Trials and Treatment Regimens

Initially, a total of nine trials that used either monochemotherapy or polychemotherapy in early-stage breast cancer were identified. Four trials were found to be ineligible for this overview because monochemotherapy regimens[2-5] had been used or because patients had received PeCT in both randomized treatment arms.[6] Table 1 lists the five known randomized trials that compared PeCT versus no PeCT that were available for this overview.[7-11] Four of these five studies compared a short course of PeCT versus no chemotherapy at all (81A, 85A, 85B, and 86A).[7,8,10,11] One study randomized patients between PeCT plus prolonged polychemotherapy (PeCT + CT) and prolonged polychemotherapy alone (CT) (81B).[9] The latter study also contained a third arm, ie, PeCT alone (413 patients); however, this arm was excluded from the analyses because there was no control arm available within the design of the study. In the majority of the studies, additional adjuvant treatment (prolonged polychemotherapy [CT] or tamoxifen [TAM]) was given based on the menopausal status and the nodal status. Generally, CT was given to premenopausal node-positive women and TAM was given to postmenopausal node-positive women. To describe the effect of adding PeCT, the original studies were subdivided and regrouped in treatment subgroups according to whether additional adjuvant treatment was mentioned in the protocol (a, PeCT *v* control; b1, PeCT

Table 1. Description of Randomized PeCT Trials Available for This Overview

Study Start Year and Code	Study Name: Description of Randomized Treatment Arms	Start Therapy (time after mastectomy)	Drugs Administered	Dose	Days of cycle
81A	Ludwig V (N−): PeCT *v* no PeCT	≤ 36 hours	Cyclophosphamide	400 mg/m^2 IV	1,8
			Methotrexate	40 mg/m^2 IV	1,8
			Fluorouracil	600 mg/m^2 IV	1,8
			Leucovorin	15 mg IV	2
				15 mg orally	9
81B	Ludwig V (N+): PeCT + CT *v* CT	PeCT: see 81A	PeCT: see 81A	PeCT: see 81A	PeCT: see 81A
		CT: 25-32 days	CT:	CT:	CT:
		(repeated every 28 days for 6 cycles)	Cyclophosphamide	100 mg/m^2 orally	1-14
			Methotrexate	40 mg/m^2 IV	1,8
			Fluorouracil	600 mg/m^2 IV	1,8
			Prednisone*	7.5 mg orally	Daily
			Tamoxifen†	20 mg orally	Daily
85A	Hamburg-study: PeCT *v* no PeCT	< 24 hours	Epirubicin	20 mg/m^2 IV	1,2
			Cyclophosphamide	300 mg/m^2 IV	1,2
85B	Genova-study PeCT *v* no PeCT	48-72 hours	Cyclophosphamide	600 mg/m^2 IV	1
			Epirubicin	60 mg/m^2 IV	1
			Fluorouracil	600 mg/m^2 IV	1
86A	EORTC 10854: PeCT *v* no PeCT	< 24 hours	Cyclophosphamide	600 mg/m^2 IV	1
			Doxorubicin	50 mg/m^2 IV	1
			Fluorouracil	600 mg/m^2 IV	1

Abbreviation: IV, intravenously.

*Administered to both premenopausal and postmenopausal women.

†Administered to postmenopausal women only.

+ CT *v* CT; b2, PeCT + TAM *v* TAM; and b3, PeCT + CT + TAM *v* CT + TAM).

Statistical Analysis

The Statistical Analysis Software (SAS; SAS Institute, Cary, NC) was used. All results are based on all available data, ie, no cutoff date for follow-up time was used. Analyses were performed on an intent-to-treat basis, that is, patients were analyzed according to their allocated treatment and the additional adjuvant treatment they were supposed to receive, a or b1 + b2 + b3, irrespective of whether they had actually received that treatment. All trials were included in the analyses, irrespective of their follow-up time. Comparisons of treatment effects were only made within a trial, following the basic "compare like with like" principle.[12] Within each of the four subdivisions (a, b1, b2, and b3), the following procedures were followed when comparing the duration of survival. Within each separate trial, the observed minus expected (O − E) number of events and its variance (V) were calculated based on a comparison of the treatment groups using a log-rank test.[12,13] For the assessment within a subgroup, values of O − E from each trial within the subgroup were added. Likewise, the variance was the sum of the individual variances of each O − E value within a subgroup. Finally, the overall results were assessed by adding the totals of the O − E and the variances over all stratification levels (eg, study within subgroup). To present these results graphically, hazards ratios (HRs = exp{(O − E)/V}), with their 95% confidence intervals (CIs) were calculated. In the graphs, the HR and CI for each individual study are represented by a black square and a horizontal line, while the HR and CI for a combination of several trials are plotted as a diamond shape. The percent reduction or increase in the HR was also calculated along with its standard deviation. Survival curves were estimated using the Kaplan-Meier method[14] and compared using the log-rank test stratified by study and treatment subgroup. The absolute survival benefit was calculated as the difference between the Kaplan-Meier survival estimates of the two treatment groups (PeCT and no PeCT) at 5 years. The variance of the survival benefit was estimated by: (VarT + VarC), where VarT and VarC are the estimated variances of the survival in the PeCT and no PeCT groups, respectively, calculated by the method of Greenwood.[15] Whenever there was a natural ordering (eg, age groups), a trend test was used to test for a trend of differences in treatment effect on the HRs in the ordered groups.[16] χ^2 tests for heterogeneity (on all treatment subgroups of all studies) and interactions (a *v* b1 + b2 + b3) were used to detect quantitative differences in treatment effect between trials.[16] Exploratory subgroup analyses were performed on predefined subgroups of age (< 50, 50 to 59, 60 to 69, 70+ years), menopausal status, and nodal status to study potential differences in the size of treatment effect within these respective groups. All *P* values referred to are two-sided.

RESULTS

Patient Characteristics

In total, individual data were available for 6,093 randomized women (1,124 deaths and 1,912 recurrences). Table 2 lists the patient characteristics according to treatment subgroups. The median follow-up duration for survival for all patients was 5.3 years (maximum, 11.3 years).

Overall Results

Figure 1 gives the disease-free survival curves for all 6,093 women in the randomized trials of PeCT versus no PeCT. Two patients appeared to have a recurrence before randomization with no further follow-up data available after randomization. To be able to include them in the analyses, their disease-free survival time was set to zero. There was a statistically significant difference in disease-free survival in favor of the PeCT arm (HR, 0.89; 95%

Table 2. Patient Characteristics According to Treatment Subgroup

	Subgroup									
	a		b1		b2		b3		Total	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	4,109		1,164		201		619		6,093	
Age, (years)										
Median	54		44		63		57		52	
Range	22-76		23-74		47-75		29-73		22-76	
Median follow-up, (years)		5.1		5.1		5.0		7.2		5.3
Menopausal status										
Pre-	1,716	42	1,087	93	0	0	145	23	2,948	48
Post-	2,393	58	77	7	201	100	474	77	3,145	52
Axillary nodal status										
Negative	3,301	80	36	3	83	41	0	0	3,420	56
Positive/unknown	808	20	1,128	97	118	59	619	100	2,673	44
No. of positive axillary nodes										
0	3,301	80	36	3	83	41	0	0	3,420	56
1-3	449	11	649	56	71	35	363	59	1,532	25
4+/negative?	359	9	479	41	47	24	256	41	1,141	19

NOTE. Group a, PeCT *v* control; b1, PeCT + CT *v* CT; b2, PeCT + TAM *v* TAM; b3, PeCT + CT + TAM *v* CT + TAM.

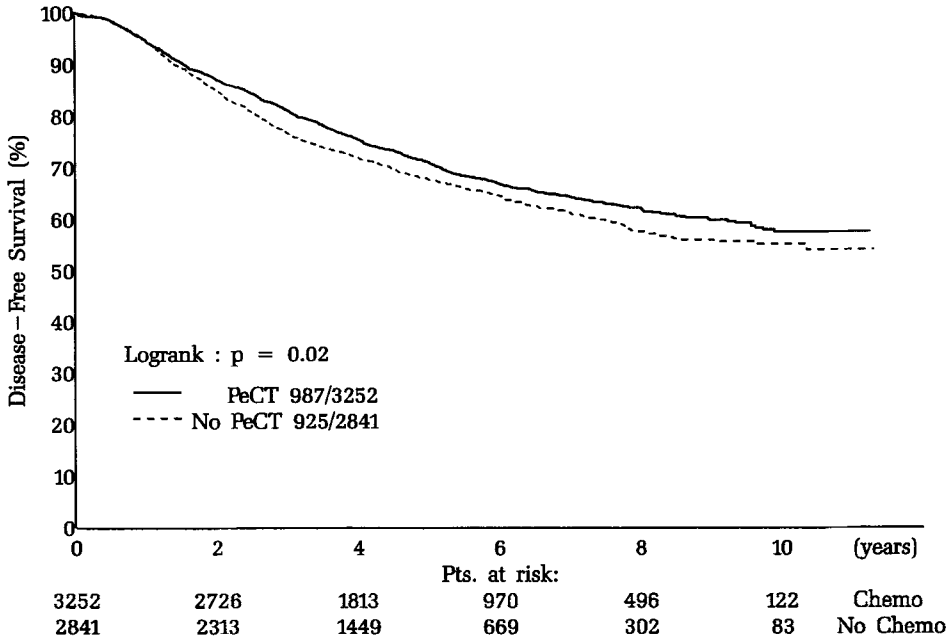

Fig 1. Disease-free survival curves for all 6,093 patients according to treatment.

CI, 0.82 to 0.98; $P = .02$) (Fig 2). At 5 years, the absolute benefit in disease-free survival (± SD) for patients randomized to the PeCT arm was 3.4% (± 1.3). When looking at (a) and (b = b1 + b2 + b3) separately, the pure comparison of (a) PeCT versus no chemotherapy showed a statistically significant decrease in the HR of 18% in favor of PeCT (HR, 0.82; 95% CI, 0.72 to 0.92; $P = .001$).

Figure 3 displays the overall survival curves for all 6,093 women. Seven toxic deaths (defined as occurring

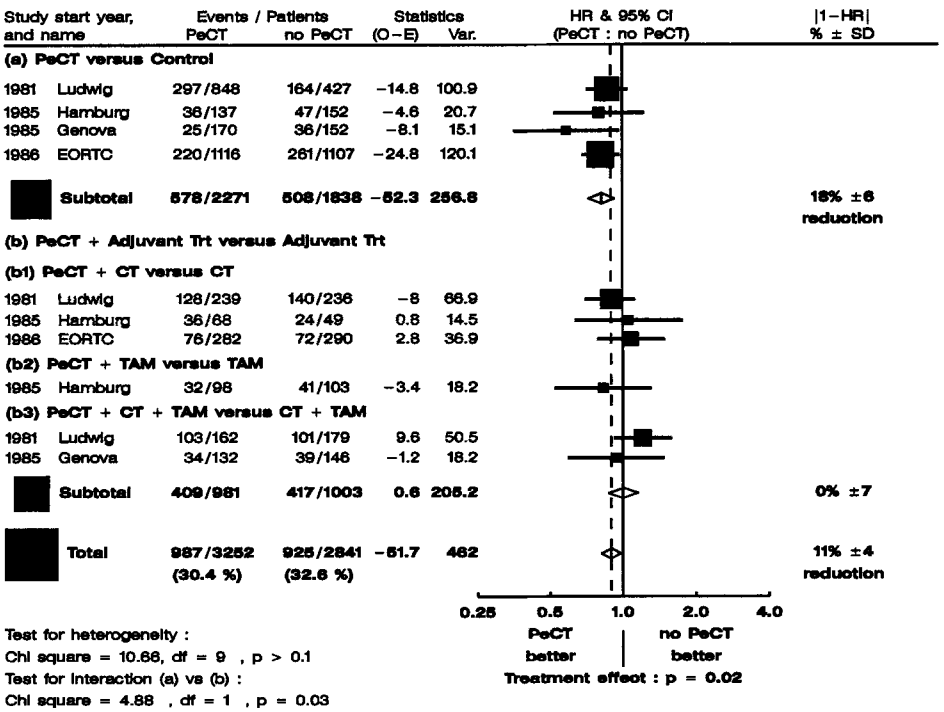

Fig 2. HR for disease-free survival for all 6,093 patients according to treatment.

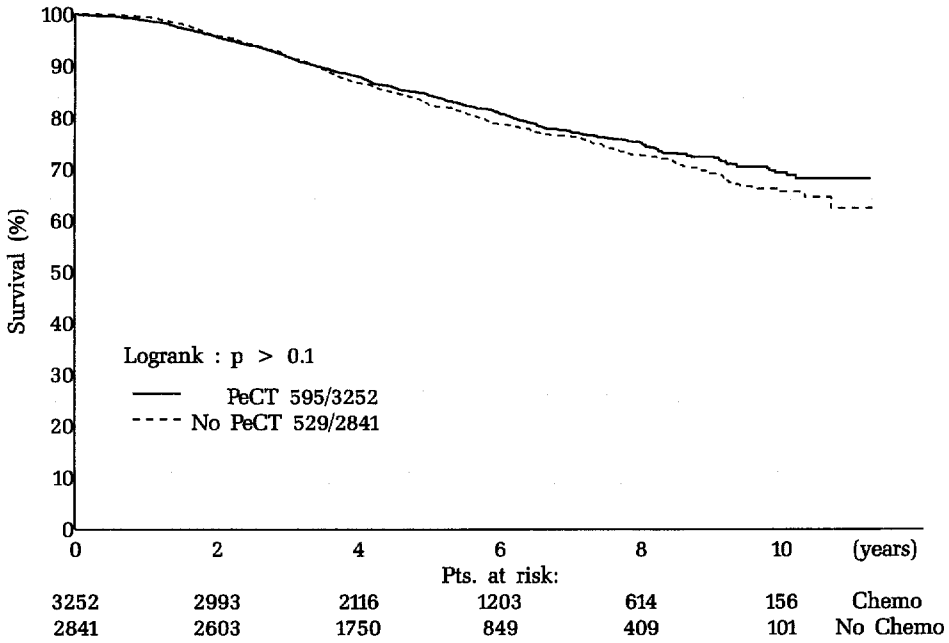

Fig 3. Survival curves for all 6,093 patients according to treatment.

within 30 days after the start of adjuvant therapy) were observed, all in the PeCT treatment arm. No statistically significant difference in overall survival between the two treatment arms was observed (HR, 0.97; 95% CI, 0.86 to 1.10; $P > .1$) (Fig 4).

Figures 5 and 6 show the HRs for local recurrence and distant metastases, respectively, for all 6,093 women randomized, according to the two different treatment subgroups. There was a significant difference in the time to local recurrence in favor of the PeCT treatment arm (HR,

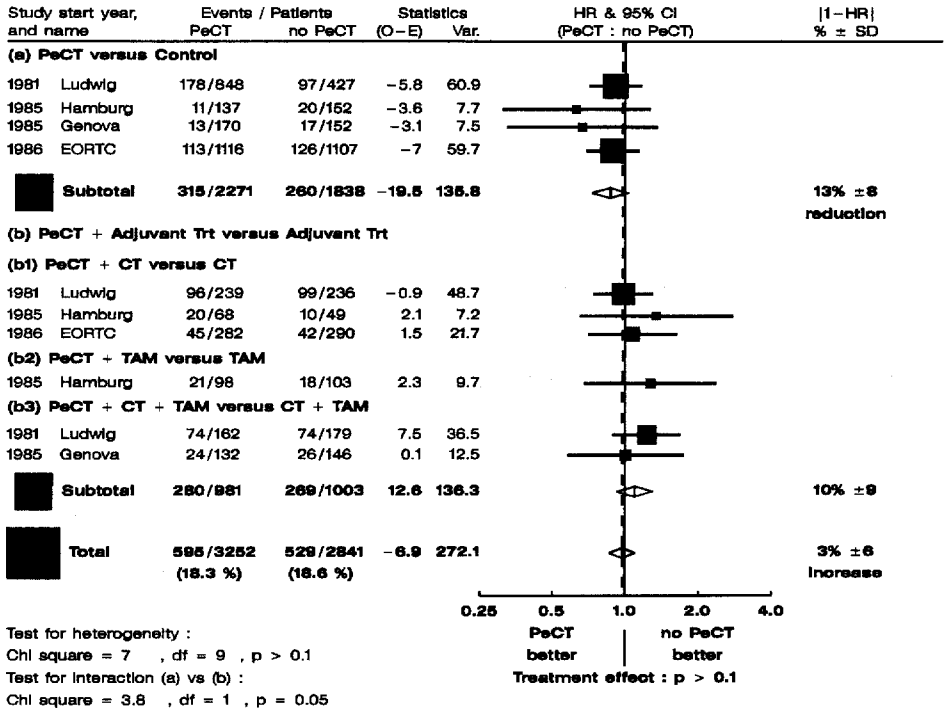

Fig 4. HR for survival for all 6,093 patients according to treatment.

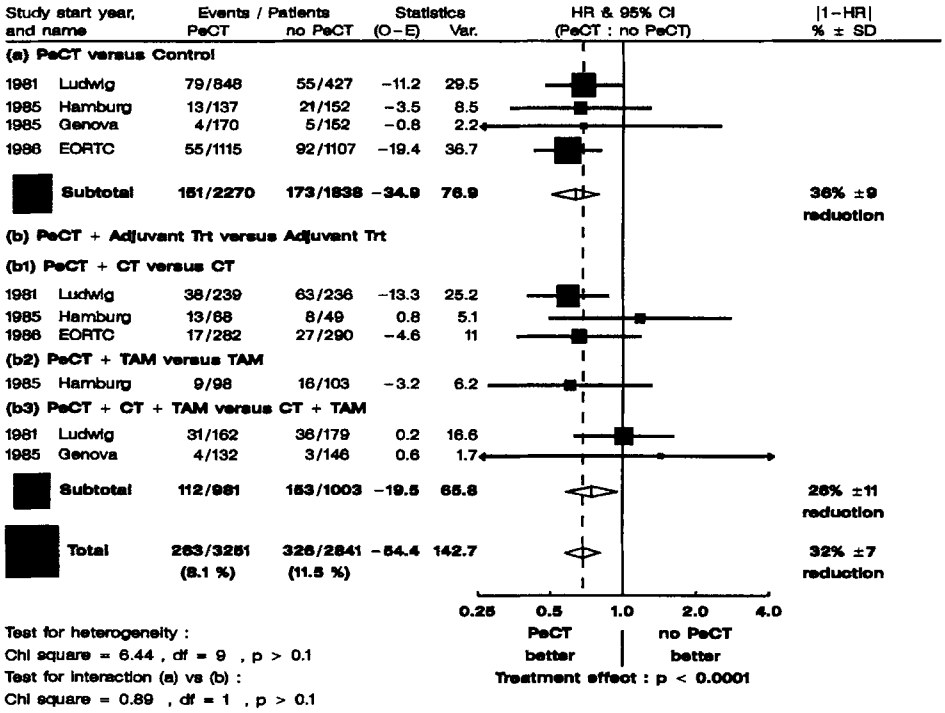

Fig 5. HR for local recurrence for all 6,093 patients according to treatment.

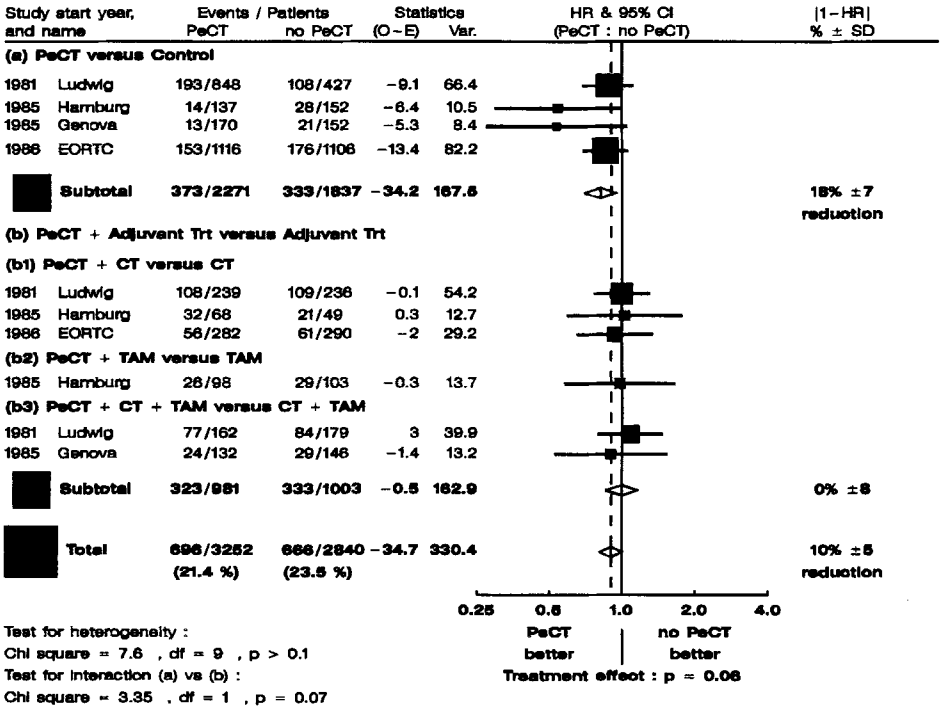

Fig 6. HR for distant metastases for all 6,093 patients according to treatment.

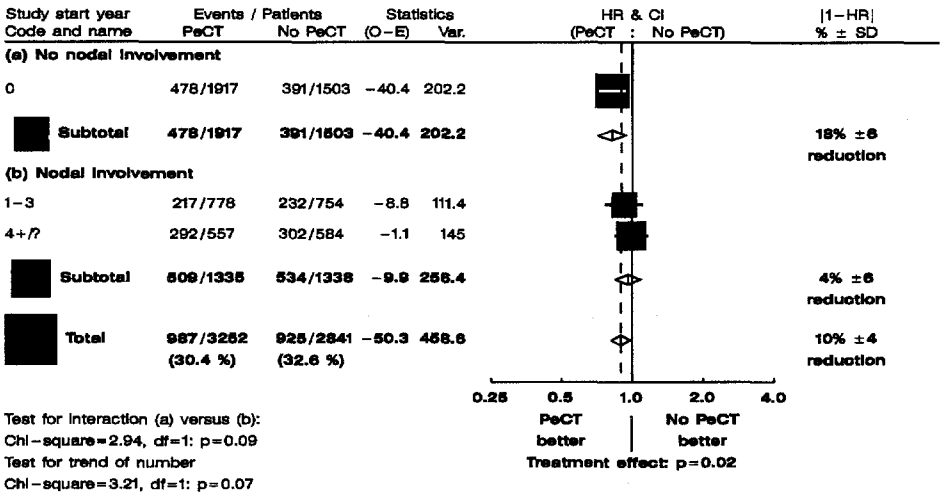

Fig 7. HR for disease-free survival for all 6,093 patients according to number of positive nodes.

0.68; 95% CI, 0.58 to 0.80; $P < .0001$) (Fig 5). The overall test for a difference in time to distant metastases of PeCT versus no PeCT was not significant (HR, 0.90; 95% CI, 0.81 to 1.00; $P = .06$) (Fig 6).

Exploratory Subgroup Analyses

Figure 7 gives the HR for disease-free survival according to the number of positive axillary nodes. The largest effect appeared to be in the women with negative nodes (HR, 0.82; 95% CI, 0.71 to 0.94; $P = .005$). For overall survival, a significant trend in treatment effect was found ($P = .04$; Fig 8), ie, PeCT appeared to be the most beneficial in node-negative patients with a possible negative effect in patients with four or more positive nodes. With respect to age and menopausal status, the largest effect of PeCT appeared in the group of premenopausal women younger than 50 years. This subgroup of patients had a reduction in HR in favor of PeCT both for disease-free survival of 17% (HR, 0.83; 95% CI, 0.7 to 0.95; $P = .009$) and for overall survival of 12% (HR, 0.88; 95% CI, 0.73 to 1.06; $P = .2$).

DISCUSSION

Based on the current follow-up data, this overview of trials of PeCT shows that starting chemotherapy perioperatively does not significantly prolong overall survival in patients with early-stage breast cancer. A significant decrease of 11% in the HR for the disease-free survival in favor of PeCT was observed when looking at all 6,093 patients. In the group of node-negative patients, there was the most benefit, namely, a decrease of 18% in the HR in favor of PeCT. This is not surprising, because in most of the trials in node-negative

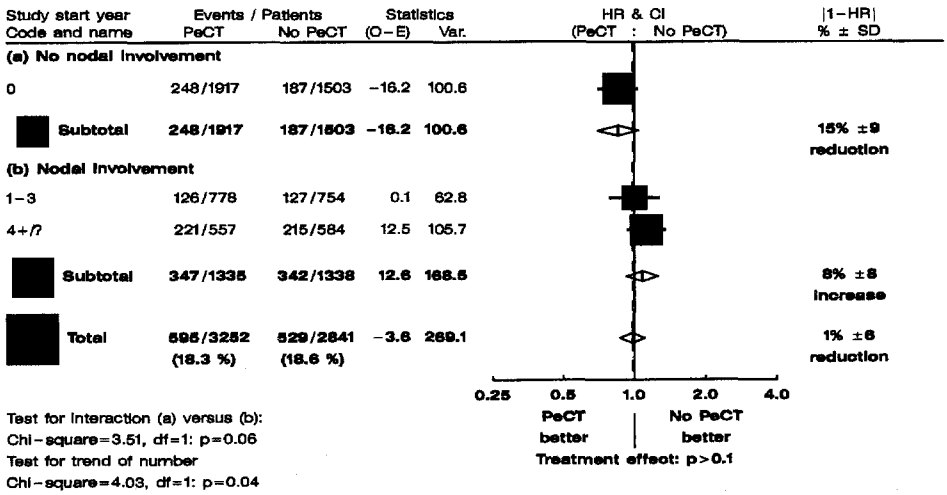

Fig 8. HR for survival for all 6,093 patients according to number of positive nodes.

patients, PeCT alone was compared with no further adjuvant therapy, whereas in trials in node-positive women, the effect of whether PeCT could add to conventionally timed adjuvant therapy was studied. Likewise, with respect to survival, patients without nodal involvement tended to show more benefit from chemotherapy compared with patients with one or more positive nodes. Our subgroup analyses confirm the results of the EBCTCG overview that chemotherapy is more effective in the group of women younger than 50 years. However, due to the limitations of subgroup analyses, it should be noted that differences within these subgroups could be due just to chance.

Our data show that perioperative chemotherapy significantly decreases the odds of locoregional recurrence by 31% in all patients ($P < .0001$). Conversely, the effect of PeCT on preventing distant metastases is much smaller (a reduction in the odds of 10%) and is not significant ($P = .06$). A similar observation was already reported in the published long-term follow-up analysis of trials of polychemotherapy in node-positive breast cancer conducted by the International Breast Cancer Study Group (IBCSG; formerly Ludwig Group).[17] In this report, the more effective (prolonged) treatments reduced the cumulative incidence of first relapse in locoregional and distant soft tissue sites from 36% to 18%. However, no alteration was seen in the incidence of first relapse of bone and visceral metastases. Likewise, in a recently published 10-year follow-up report of a trial (EORTC 09771) that compared a low-dose prolonged polychemotherapy regimen versus no further therapy in stage II breast cancer patients, a 37% reduction in the odds of locoregional recurrence was observed in the chemotherapy arm, whereas no significant reduction could be demonstrated for the time to distant metastases.[18] In both of these reports, a significant advantage in terms of overall survival was observed for the chemotherapy arm, despite the lack of a significant effect of chemotherapy on the distant metastases. Compared with the results of these long-term regimens, the effect of PeCT on the time to local recurrence observed in this overview is remarkable. However, the question of whether this advantage for the PeCT arm will eventually be translated into a prolonged overall survival benefit can only be answered with more follow-up evaluation.

This overview suggests that adding PeCT does not improve the effect of other adjuvant therapies in node-positive patients, which has been reported earlier by the IBCSG.[9] On the other hand, the advantage for the PeCT treatment arm in terms of a prolonged disease-free survival in the very large group of node-negative patients demonstrates once more that adjuvant chemotherapy is able to change the course of breast cancer in patients with an already favorable prognosis.

At present, there is sufficient evidence that adjuvant chemotherapy can reduce the risk of relapse in node-negative patients with early-stage breast cancer.[1] However, it is still unclear for a large group of node-negative patients whether they really should receive a more aggressive treatment, even though there are extremes of high and low risk where it is possible to make recommendations about adjuvant systemic chemotherapy outside the context of clinical trials.[19] Our results show that a short intensive course of PeCT can already yield a significant effect in node-negative patients with early-stage breast cancer. Results of future clinical trials in node-negative patients will show whether long-term treatment can further improve these results, taking into account other important factors like treatment-related toxicity and possible effects on quality of life. Until then, all patients who are candidates for these clinical trials should be offered the opportunity to participate.[19]

APPENDIX
Participating Members and Institutions

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REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. Lancet 339:1-15, 71-85, 1992

2. Fisher B, Slack N, Katrych D, et al: Ten-year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynecol Obstet 140:528-534, 1975

3. Kjellgren K, Nissen-Meyer R, Norin T: Perioperative adjuvant chemotherapy in breast cancer. The Scandinavian adjuvant chemotherapy study 1. Acta Oncol 28:899-901, 1989

4. Houghton J, Baum M, Nissen-Meyer R: Is there a role for perioperative adjuvant therapy in the treatment of early breast cancer? Eur J Surg Oncol 14:227-233, 1988

5. Baum M, Houghton J, Riley D: Results of the Cancer Research Campaign adjuvant trial for perioperative cyclophosphamide and long-term tamoxifen in early breast cancer reported at the tenth year of follow-up. Cancer Research Campaign Breast Cancer Trials Group. Acta Oncol 31:251-257, 1992

6. Nissen-Meyer R, Høst H. Kjellgren K: Prolonged adjuvant chemotherapy in breast cancer. The Scandinavian adjuvant chemotherapy study 2. Acta Oncol 28:903-906, 1989

7. Ludwig Breast Cancer Study Group: Prolonged disease-free survival after one course of perioperative adjuvant chemotherapy for node-negative breast cancer. N Engl J Med 320:491-496, 1989

8. Goldhirsch A, Castiglione M, Gelber RD: A single perioperative adjuvant chemotherapy course for node-negative breast cancer: Five year results of trial V. International Breast Cancer Study Group (formerly Ludwig Group). Monogr Natl Cancer Inst 11:89-96, 1992

9. Ludwig Breast Cancer Study Group: Combination adjuvant chemotherapy for node-positive breast cancer. Inadequacy of a single perioperative cycle. N Engl J Med 319:677-683, 1988

10. Sertoli MR, Pronzato P, Rubagotti A, et al: Perioperative polychemotherapy for primary breast cancer: A randomized study. Proc Am Soc Clin Oncol 10:48, 1991 (abstr)

11. Clahsen PC, van de Velde CJH, Julien JP, et al: Perioperative adjuvant chemotherapy in early breast cancer patients, EORTC study 10854. Breast Cancer Res Treat 27:132, 1993 (abstr)

12. Yusuf S, Peto R, Lewis J, et al: Beta blockade during and

after myocardial infarction: An overview of the randomized trials. Prog Cardiovasc Dis 27:335-371, 1985

13. Early Breast Cancer Trialists' Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. N Engl J Med 319:1681-1692, 1988

14. Kaplan EL, Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

15. Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data. New York, NY, Wiley, 1980

16. Early Breast Cancer Trialists' Collaborative Group: Treatment of Early Breast Cancer, vol 1: Worldwide Evidence 1985-1990. Oxford, United Kingdom, Oxford University, 1990

17. Goldhirsch A, Gelber RD, Price KN, et al: Effect of systemic adjuvant treatment on first sites of breast cancer relapse. Lancet 343:377-381, 1994

18. Clahsen PC, van de Velde CJH, Welvaart K, et al: Ten-year results of a randomized trial evaluating prolonged low-dose adjuvant chemotherapy in node-positive breast cancer. J Clin Oncol 13:33-41, 1995

19. Veronesi U: NIH consensus meeting on early breast cancer. Eur J Cancer 26:843-844, 1990