Impact of age, tumor characteristics, and treatment on local control and disease outcome in early stage breat cancer : an EORTC translational research project

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CHAPTER 3

Preoperative Chemotherapy in Primary Operable Breast Cancer: Results From the European Organization for Research and Treatment of Cancer Trial 10902

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Abstract

Purpose:
To evaluate whether preoperative neoadjuvant chemotherapy in patients with primary operable breast cancer results in better overall survival (OS) and relapse-free survival rates and whether preoperative chemotherapy permits more breast-conserving surgery procedures than postoperative chemotherapy.
Patients and Methods:
Six hundred ninety-eight breast cancer patients (T1c, T2, T3, T4b, N0 to 1, and
M0) were enrolled onto a randomized phase III trial that compared four cycles of fluorouracil, epirubicin, and cyclophosphamide administered preoperatively versus the same regimen administered postoperatively (the first cycle administered within 36 hours after surgery). Patients were followed up for OS, progression free survival (PFS), and locoregional recurrence (LRR).
Results:
At a median follow-up of 56 months, there was no significant difference in terms of OS (hazards ratio: 1.16; P = 0.38), PFS (hazards ratio: 1.15; P = 0.27), and time to LRR (hazards ratio: 1.13; P = 0.61). Fifty-seven patients (23%) were downstaged by the preoperative chemotherapy, whereas 14 patients (18%) underwent mastectomy and not the planned breast-conserving therapy.
Conclusion:
The use of preoperative chemotherapy yields similar results in terms of PFS, OS, and locoregional control compared with conventional postoperative chemotherapy. In addition, preoperative chemotherapy enables more patients to be treated with breast-conserving surgery. Because preoperative chemotherapy does not improve disease outcome compared with postoperative chemotherapy, future trials should involve
quality-of-life studies to investigate whether patients will benefit from this treatment modality.

Introduction

Trials that studied the role of adjuvant chemotherapy in the management of primary operable breast cancer conducted during the 1970s and 1980s showed significant improvements in progression-free and overall survival [1]. Conventionally, adjuvant systemic therapy is administered after local treatment in early breast cancer [2]. However, since the introduction of conservative treatment modalities, there has been considerable interest in the efficacy of preoperative chemotherapy to decrease tumor size. One of the potential benefits of preoperative chemotherapy is the more frequent usage of breast-conserving treatment modalities. Moreover, it has been hypothesized that preoperative chemotherapy has a more powerful effect on survival compared with postoperative chemotherapy. The rationale for these hypotheses comes from several biologic premises. Findings in various animal models [3-5] showed an increase of labeling index in residual tumor cells as well as an increase of circulating growth-stimulating factors after the removal of the primary tumor in murine models. In these models, adjuvant systemic therapy administered before the removal of the primary tumor impaired this increase in cell-kinetic mechanisms [6,7].
In addition, Goldie and Coldman [8] developed a hypothesis, which implies that as a tumor cell population increases, an ever-expanding number of drug-resistant

phenotypic variants arise as a result of spontaneous somatic mutations. Although the merits of preoperative chemotherapy in the treatment of locally advanced breast cancer are well established, the feasibility of preoperative chemotherapy in early breast cancer is still a matter of discussion.
The European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group started a randomized trial in 1991 to investigate the value of preoperative chemotherapy in early breast cancer, EORTC trial 10902. The primary objective of this trial was to test whether preoperative chemotherapy yields better results in terms of progression-free and overall survival than the same chemotherapeutic regimen administered postoperatively. Another objective was to study whether preoperative chemotherapy would permit more breast-conserving therapies by reducing primary tumor size. A third objective was to determine whether preoperative chemotherapy resulted in better locoregional control, especially after breast-conserving surgery.
An additional objective of the study was to evaluate the response of the primary tumor to preoperative chemotherapy and to correlate this response to disease-free and overall survival. This report compares the outcome of 698 women with early breast cancer randomized to receive either preoperative chemotherapy or the same regimen administered postoperatively.

Patients and methods

Patient Characteristics
Between April 1991 and May 1999, 698 women were enrolled onto the EORTC study 10902 in 17 institutions in 14 countries. Patients had primary operable breast cancer (T1c, T2, T3, T4b, N0 to 1, and M0). Breast cancer was preferably diagnosed by core needle biopsy (CNB) or by fine-needle aspiration cytology as part of triple diagnosis. For the diagnosis of T1c tumors, CNB was mandatory. CNB was also mandatory in case of doubt or suspicion of carcinoma-in-situ after fine-needle aspiration. Exclusion criteria consisted of age older than 70 years; bilateral breast cancer; previous treatment for breast cancer; presence of distant metastases; pregnancy or lactation at the time of diagnosis; previous or current other malignancies except adequately treated basal or squamous carcinoma of the skin or cervix uteri; World Health Organization performance status more than 2; active cardiac disease; and severe hematologic, renal, or hepatic abnormalities. All patients gave informed consent before entering onto the trial. Randomization was performed centrally by the EORTC Data Center. At randomization, patients were stratified for institution, age (50 years or 50 years), clinical tumor size, clinical nodal status (N or N), and planned type of surgery (mastectomy or breast-conserving surgery). Patients 50 years old or younger were considered to be premenopausal, and those older were deemed postmenopausal. Tumor estrogen receptor (ER) status was estimated by the ligand binding assay technique or by the immunohistochemistry technique. For the ligand binding assay, a concentration $\geq$ 10 fmol ER/mg protein was considered positive, and a value lower than 10 fmol ER/mg protein was considered negative. If the ER status was measured by immunohistochemistry, positivity or negativity was determined according to the scoring systems used by the individual institutions. There was no

standardization of the assay, so general cutoff points cannot be given for immunohistochemistry (EORTC Manual for Clinical Research in Breast Cancer) [9].

Treatment

Treatment consisted of surgery in combination with either preoperative or postoperative chemotherapy. Surgery consisted of either a modified radical mastectomy or breast-conserving surgery (wide local excision of the tumor or quadrantectomy plus axillary dissection and adjuvant radiotherapy). Before treatment, investigators had to report which type of surgery was indicated at the time of diagnosis. Subsequently, the planned type of surgery and performed type of surgery were compared to investigate whether preoperative chemotherapy induced a higher rate of breast-conserving surgery. Guidelines and selection criteria that concerned surgery were given in the study protocol, but patient selection for breast-conserving therapy was ultimately left up to the treating surgeon.

Chemotherapy consisted of four cycles of preoperative fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, and cyclophosphamide 600 mg/m^2 (FEC) administered intravenously, at intervals of every 3 weeks. In the preoperative chemotherapy group, surgical therapy followed within 4 weeks of the fourth course of chemotherapy. In the postoperative chemotherapy group, the first cycle was administered within 36 hours after surgery, as has been advocated before [10,11]. Administration of FEC was delayed for a maximum of 2 weeks as a result of either hematologic, hepatic and renal, or gastrointestinal toxicities on day 1 of any cycle. Dose modifications were assessed according to the guidelines stipulated by the EORTC Breast Cancer Cooperative Group [9].

Adjuvant radiotherapy was administered after surgery in the preoperative chemotherapy group. In the postoperative chemotherapy group, it was decided to administer irradiation after the completion of chemotherapy. This way, radiotherapy did not interfere with the chemotherapeutic regimen, in which the first course was to be administered preoperatively. All patients who underwent breast-conserving therapy received irradiation of the whole breast. Other recommended guidelines for radiotherapy, as stipulated in the protocol, consisted of chest wall and parasternal irradiation in patients with an initial tumor of 5 cm or more in its largest dimension and irradiation of the infraclavicular and supraclavicular fossa in patients with a positive infraclavicular node after lymph node dissection. Radiotherapy was indicated in all cases where surgery was not considered to be radical. Specified dose at the target volume was 50 gray, administered in four or five weekly fractions in 5 weeks. For the parasternal/infrasupraclavicular fossa and chest wall, at least 45 Gy had to be administered in four or five weekly fractions in 4.5 to 5 weeks. However, some hospitals used their own radiation protocol. Patients $\geq$ 50 years of age also received tamoxifen 20 mg daily for at least 2 years, regardless of their ER and nodal status.

End Points

The primary end point of this study was overall survival. Survival time was defined as the time between randomization and death from any cause. Secondary end points were progression-free survival and locoregional recurrence. Progression-free survival was defined as the time between the date of randomization and the date of disease relapse (including distant metastases, locoregional recurrences, secondary primary

tumors, and contralateral breast cancers) or death, whichever came first. Locoregional recurrence was defined as a recurrence in the ipsilateral breast or in the ipsilateral regional lymph nodes, including supraclavicular nodes. Time to locoregional recurrence was defined as the time between date of randomization and locoregional recurrence, regardless of whether the locoregional recurrence was the first event or not. It is well known that the administration of adjuvant chemotherapy is a considerable burden to the patient in terms of quality of life. However, not many data are available that concern the effects of preoperative chemotherapy on quality of life compared with conventional postoperative chemotherapy. Therefore, a quality-of-life study program was set up that was, however, unsuccessful as a result of poor compliance.

Tumor Response

Clinical tumor size and nodal status were estimated before the start of chemotherapy as well as at the time of surgery by both palpation and mammography. The product of the two greatest perpendicular diameters was used to compare tumor size before and after chemotherapy, as defined by the International Union Against Cancer criteria [12]. A clinical complete response (cCR) was considered a complete disappearance of all clinically detectable malignant disease by palpation as well as mammography. Tumor specimens from patients who underwent preoperative chemotherapy were examined for the presence of microscopic residual tumor to correlate the clinical absence of tumor with pathologic evaluation. If no signs of residual malignant cells at the primary site and axillary lymph nodes were seen with histologic examination, this was scored as a pathologic complete response (pCR). Clinical tumor response to preoperative chemotherapy was assessed at the time of surgery. If the tumor had become undetectable before completion of the four cycles of preoperative chemotherapy, chemotherapy was continued as outlined in the protocol. Clinical partial response was defined as 50% decrease in total tumor size after four cycles of preoperative chemotherapy at the time of surgery. An increase of 25% in tumor size after a minimum of two courses of preoperative chemotherapy was considered to be progressive disease (PD).

In patients with clinically negative nodes at randomization, the development of palpable nodes during the administration of preoperative chemotherapy was considered evidence of PD. After a diagnosis of PD, patients immediately underwent surgery before completing the preoperative chemotherapy schedule. If the PD was not primary operable, the patient was declared to have experienced treatment failure, and subsequent treatment was left to the discretion of the responsible clinician. If patients did not meet one of the above-mentioned criteria after four cycles of chemotherapy, they were classified as having stable disease.

Follow-Up

All patients were followed up until death. In the first 2 years after surgery, patients were seen at least every 6 months and, in the following 3 years, every 6 to 12 months. Minimal requirements for follow-up were physical examination, locoregional evaluation, and performance scale assessment, with mammography, chest x-ray, and alkaline phosphatase and lactate dehydrogenase measurements every year postoperatively. One institute used CA 15-3 measurements instead of lactate dehydrogenase.

Characteristic	Total		Preoperative Chemotherapy		Postoperative Chemotherapy	
	No.	%	No.	%	No.	%
Total patients	698		350		348	
Age						
≤ 50 years	385	55.2	192	54.9	193	55.5
> 50 years	313	44.8	158	45.1	155	44.5
Axillary nodal status*						
Negative	333	47.7	171	48.8	162	46.6
Positive	355	50.9	176	50.3	179	51.4
Unknown	10	1.4	3	0.9	7	2.0
Tumor size†						
≤ 2 cm	96	13.8	49	14.0	47	13.5
> 2 cm	592	84.8	298	85.1	294	84.5
T4b	36	5.2	22	6.3	14	4.0
Unknown	10	1.4	3	0.9	7	2.0
ER status						
Negative	141	20.2	60	17.2	81	23.3
Positive	337	48.3	159	45.4	178	51.1
Unknown	220	31.5	131	37.4	89	25.6
Planned surgical procedure						
Mastectomy	536	76.8	268	76.6	268	77.0
Lumpectomy	151	21.6	77	22.0	74	21.3
No surgery	11	1.6	5	1.4	6	1.7
Additional radiotherapy						
Yes	452	64.8	237	67.7	215	61.8
No	246	35.2	113	32.3	133	38.2
Additional hormonal therapy						
Yes	273	60.9	139	39.7	134	38.5
No	425	39.1	211	60.3	214	61.5

*Clinical nodal status.
†Clinical tumor size.

Table 1. Baseline Patient Characteristics

Statistical Aspects

All analyses were based on the intent-to-treat principle. The two treatment arms were compared by the log-rank test for the time-to-event end points. The differences between the two treatment groups were graphically depicted by Kaplan and Meier curves. As it seemed from literature studies that both nodal and menopausal status could have a substantial impact on the treatment comparison, it was decided before the start of the analysis to perform subgroup analyses for these two variables. The nominal significance level for each subgroup analysis was adjusted by the Bonferroni method. Thus, in the cases of the four subgroup analyses for nodal and menopausal status, the nominal significance level for each of the subgroup analyses was set at .0125 (.05 divided by 4). The trial was designed to detect a 10% survival difference at 5 years (from 75% to 85%) with 80% power, for which 102 events were needed.

Results

Patients

Of the 698 patients, 350 patients were randomized to receive preoperative chemotherapy, and 348 patients were randomized to the postoperative chemotherapy group (first cycle of FEC administered within 36 hours after surgery). Tumor and patient characteristics were well distributed between the two treatment arms

Event	Preoperative Chemotherapy (n = 350)	Postoperative Chemotherapy (n = 348)
Cardiac function		
No dysfunction	297	289
Asymptomatic dysfunction	19	16
Symptomatic dysfunction, no therapy needed	1	5
Symptomatic dysfunction, responsive to therapy	1	3
Nausea/vomiting		
None	49	46
Nausea	89	85
Transient vomiting	119	125
Vomiting requiring therapy	69	62
Intractable vomiting	2	2
Diarrhea		
None	288	278
< 2 days	30	35
> 2 days	10	6
Requiring therapy	–	1
Drug fever		
None	299	283
< 38 °C	20	25
38-40 °C	8	9
> 40 °C	–	–
Fever with hypotension	–	1
Alopecia		
None	23	21
Minimal hair loss	65	37
Moderate patchy alopecia	68	68
Complete reversible alopecia	148	172
Drug allergy		
None	311	307
Edema	12	11
Bronchospasm, no therapy needed	1	1
Bronchospasm, therapy needed	1	–
Oral toxicity		
None	222	242
Erythema	59	45
Erythema/ulcers, normal dietary intake	31	22
Erythema/ulcers, requiring liquid diet	2	2
Thromboembolic complications		
None	314	305
Superficial phlebitis	1	1
Deep phlebitis	–	1
Embolism	–	–
No data	35	41

Table 2. Overall toxicity distribution

(Table 1), except for breast-conserving surgery rates, which were, as expected, higher in the preoperative chemotherapy group. Twenty-one patients were considered ineligible because of inadequate staging (n = 17), a World Health Organization performance status more than 2 (n = 3), or age greater than 70 years (n = 1).

Chemotherapy

Overall, 635 patients (91%) received the planned chemotherapy dose (321 patients [92%] in the study arm and 314 patients [90%] in the control arm). Sixty-three patients (8%) received less than 75% of the planned dose. Nineteen patients (3%) who began chemotherapy did not complete it (11 patients [3%] in the study arm and eight patients [2.5%] in the control group). Thirty-eight patients who were randomized to the preoperative chemotherapy group underwent treatment modification because of treatment-related febrile neutropenia versus 44 patients in the postoperative chemotherapy group. No treatment-related deaths were reported. An overview of chemotherapy-related toxicity is given in Table 2. Furthermore, four patients who were randomized to receive postoperative chemotherapy received preoperative chemotherapy, and three patients who were randomized to receive preoperative chemotherapy received postoperative chemotherapy. Forty patients did not receive chemotherapy. Of these patients, 16 patients were deemed ineligible. Eight patients refused chemotherapeutic treatment, two patients in the postoperative chemotherapy group did not receive chemotherapy as stipulated by the protocol because of postoperative complications, and seven patients did not receive chemotherapy for unknown reasons. From a further seven patients, no information that concerned treatment specifications or follow-up was received, even after repeated queries. Unfortunately, for approximately 30% of the patients, information that concerned ER status was missing. This was partly a result of the fact that this information was not mandatory and that tamoxifen was given irrespective of ER status in patients ≥ 50 years of age.

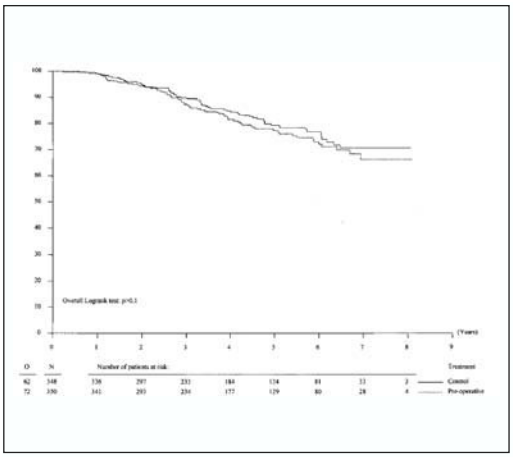

Figure 1. Overall survival

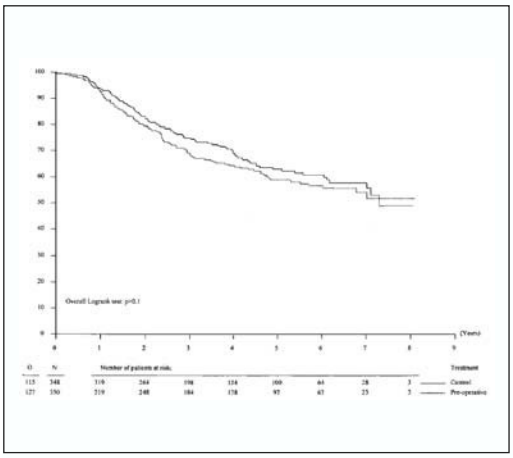

Figure 2. Time to disease progression or death

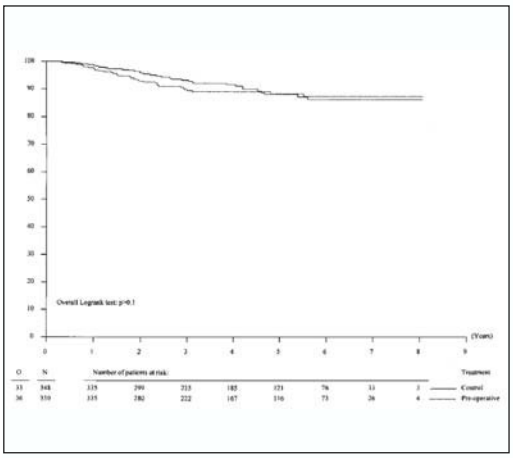

Figure 3. Locoregional recurrence rate

Surgery

Four hundred sixty-five patients underwent modified radical mastectomy, and 199 patients underwent breast-conserving surgery. Nineteen patients who underwent lumpectomy did not receive adjuvant radiotherapy. Thirty-eight percent of the patients on the study arm who were treated with mastectomy received radiotherapy, and 43% of the patients on the control arm who were treated with mastectomy received radiotherapy.

In the preoperative chemotherapy group, 20 patients did not receive the surgical treatment stipulated by the study protocol, versus 14 patients in the postoperative group. At the time of axillary clearance, at least six nodes had to be obtained for pathologic examination, and in 77% of the patients entered onto the study, 10 or more axillary nodes were examined. Surgical complications consisted of 16 grade 1/2 wound infections in the preoperative chemotherapy group, versus 25 grade 1/2 wound infections and two grade 3/4 wound infections in the postoperative chemotherapy group that required antibiotic treatment. Anticoagulant prophylaxis was administered on the basis of experience from previous trials that studied the efficacy of perioperative chemotherapy [13,14]. No severe postsurgical thromboembolic complications were observed in the postoperative chemotherapy group.

Overall Survival, Progression-Free Survival, and Locoregional Recurrence

Of the 698 randomized patients, 232 experienced relapse, from which 124 patients died. Furthermore, 10 patients died without experiencing a relapse. No significant differences between the two treatment arms were observed for progression-free and overall survival.

Tumor Response	Patients Randomized to Preoperative Chemotherapy No.	%
CR	23	6.6
PR	148	42.3
No change	139	39.7
Progression of disease	5	1.4
Not assessable	16	4.6
No preoperative chemotherapy*	19	5.4

*Six ineligible patients; 10 patients refused treatment; three patients received postoperative chemotherapy.

Table 3. Clinical Tumor Response

	Patients Randomized to Preoperative Chemotherapy							
	T1 (n = 49)		T2 (n = 197)		T3/T4 (n = 101)		Unknown (n = 3)	Total (N = 350)
	No.	%	No.	%	No.	%	No.	No.
pT0/pTis	–	–	10	5	5	5	–	15
pT1	44	90	88	45	17	17	–	149
pT2	3	6	76	39	42	41	–	121
pT3/pT4	–	–	3	1	24	24	–	27
pTx	2	4	20	10	13	13	3	38

Table 4. Clinical tumor size vs. pathological tumor size after pre-operative chemotherapy

Overall survival after 4 years was 82% in the preoperative group and 84% in the postoperative group (hazards ratio [HR], 1.16; 95% confidence interval [CI], 0.83 to .63; *P* = 0.38) (Fig 1). Progression-free survival rates after 4 years for the preoperative and postoperative groups were 65% and 70%, respectively (HR, 1.15; 95% CI, 0.89 to 1.48; *P* = 0.27) (Fig 2). To date, 69 patients have experienced a locoregional recurrence, 36 in the preoperative chemotherapy group and 33 in the postoperative chemotherapy group. Time to locoregional recurrence was not significantly different between the two treatment arms (HR, 1.13; 95% CI, 0.70 to 1.81; *P* = 0.61) (Fig 3). Sixty-two of these patients experienced a locoregional recurrence as first event. Subgroup analyses were performed in an exploratory way for nodal status and menopausal status. The largest difference was found in clinical node-negative patients (n = 385) in terms of overall survival (HR, 1.77; 95% CI, 1.03 to 3.02; *P* = 0.04) and progression-free survival (HR, 1.53; 95% CI, 1.03 to 2.28; *P* = 0.03) in favor of the postoperative chemotherapy group. These *P* values failed to be significant compared with the adjusted nominal significance level of 0.0125.

Tumor Response

Table 3 shows the clinical tumor response after chemotherapy. An overall objective response was observed in 49% of the patients randomized to the preoperative chemotherapy group. Twenty-three patients (6.6%) experienced a cCR and progression of disease was seen in five patients (1.4%). Of the twenty-three patients who experienced a cCR, only six patients did not have any invasive tumor left. Apart from the six patients who experienced a pCR in accordance with the clinical assessment, seven other patients were microscopically free of tumor at the primary site and axilla after four cycles of preoperative chemotherapy but were not classified as having a cCR. The thirteen patients without evidence of residual malignancy do have a significant advantage in terms of overall survival (HR, 0.86; 95% CI, 0.77 to 0.96; *P* = 0.008) compared with patients who still had residual tumor cells left after preoperative chemotherapy.

Next, we tested the prognostic significance of clinical objective tumor response in terms of survival in a multivariate model together with clinical tumor size, clinical nodalstatus, and ER status. Clinical objective response, however, was not a significant prognostic factor. Table 4 shows the correlation between clinical tumor sizebefore preoperative chemotherapy and pathologic tumor size after preoperative chemotherapy. Both in the preoperative and postoperative arms, 14% of the patients had a clinical tumor size less than 2 cm at the time of diagnosis. After four courses of preoperative chemotherapy, 47% of the patients had a pathologic tumor size less than

	Patients Randomized to Preoperative Chemotherapy							
	N0 (n = 171)		N1 (n = 164)		N2 (n = 12)		Unknown (n = 3)	Total (N = 350)
	No.	%	No.	%	No.	%	No.	No.
pN0	95	56	36	22	2	17	–	133
pN1	64	37	121	74	8	66	–	193
pN2	–	–	–	–	2	17	–	2
pN unknown	12	7	7	4	–	–	3	22

Table 5. Clinical nodal status vs. pathological nodal status after pre-operative chemotherapy

	Preoperative Chemotherapy (n = 350)		Postoperative Chemotherapy (n = 348)	
Pathologic Tumor Size	No.	%	No.	%
T0	15	4	4	1
T1	149	43	88	25
T1 + T0	164	47	92	26
T2	121	35	173	50
T3	19	5	40	11
T4	8	2	12	3
Tx	38	11	31	10

Table 6. Differences in pathological tumor size between both study-arms

No. of Pathologic Positive Lymph Nodes	Preoperative Chemotherapy		Postoperative Chemotherapy	
	No.	%	No.	%
N0	134	38	111	32
N1-3	109	31	122	35
N4+	84	24	97	28
Other	23	7	18	5

Table 7. Differences in pathological nodal status between both study-arms

	Patients Randomized to Preoperative Chemotherapy				
	Performed MRM		Performed BCT		
	No.	%	No.	%	Total
Planned MRM	189	77	57	23	246
Planned BCT	14	18	63	82	77
Total	203	–	120	–	323

Abbreviations: BCT, breast-conserving therapy; MRM, modified radical mastectomy.

Table 8. Planned versus performed type of surgery

2 cm, whereas 26% of the patients in the postoperative arm had a pathologic tumor size less than 2 cm. Nodal status characteristics are listed in Table 5. At the time of diagnosis, 49% of the patients in the preoperative group and 47% of the patients in the postoperative group had clinical negative axillary lymph nodes. Pathologic examination after surgery showed a lower percentage of negative axillary lymph nodes in both the preoperative and the postoperative group 38% and 35%, respectively. Differences in pathologic tumor size and axillary nodal status between both study arms are listed in Table 6 and Table 7.

Downstaging

Before treatment, investigators had to report whether mastectomy or breast-conserving surgery was indicated. In the preoperative chemotherapy group, the rate of breast-conserving therapy was higher than in the postoperative chemotherapy group. In the preoperative chemotherapy group, 57 patients (23%) underwent breast-conserving surgery and not the planned mastectomy (Table 8), versus 14 patients (18%) who underwent mastectomy and not the planned breast-conserving surgery.

In the preoperative chemotherapy group, all patients who underwent breast-conserving surgery were compared according to their planned type of surgery. Patients who were planned for mastectomy but underwent breast-conserving therapy because of down-staging of the tumor did worse in terms of overall survival (HR, 2.53; 95% CI, 1.02 to 6.25) compared with patients who were initially planned to receive breast-conserving therapy and were treated accordingly (Fig 4), which suggested a relation between the outcome of locoregional treatment and tumor response. This, however, is not a randomized comparison. The observed difference in disease outcome might be a result of a selection bias as a result of different patient characteristics in the two groups. Therefore, we evaluated patient characteristics to detect potential differences. Of the patients who were downstaged, 35% were clinically node-negative before the start of chemotherapy versus 46% in the group in which breast-conserving therapy

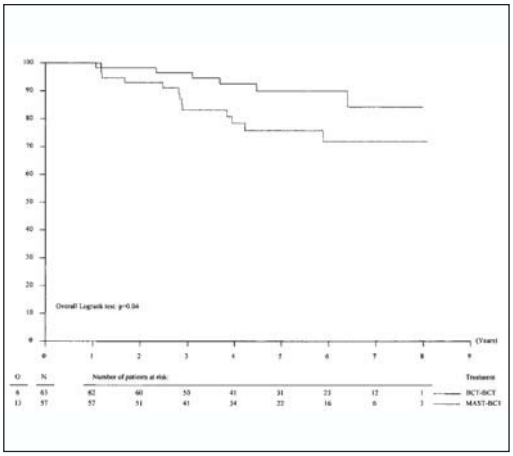

Figure 4. Survival in planned versus downstaged mastectomy

Characteristic	BCT ⇒ BCT No.	BCT ⇒ BCT %	MRM ⇒ BCT No.	MRM ⇒ BCT %
Total patients, N = 120	63		57	
Deaths	6	9.5	13	23
Age				
≤ 50 years	31	49	35	61
> 50 years	32	51	22	39
Clinical nodal status				
Negative	29	46	20	35
Positive	34	54	37	65
Clinical tumor size				
≤ 2 cm	49	78	44	77
> 2 cm	14	22	13	23
Pathologic nodal status				
Negative	32	51	36	63
Positive	31	49	21	37
Pathologic tumor size*				
≤ 2 cm	49	79	41	75
> 2 cm	13	21	14	25
ER status				
Negative	8	13	9	15
Positive	34	54	26	46
No data	21	33	22	39
Tumor response				
Overall response, cCR + cPR	39	62	44	77
No change	19	30	12	21
Progression of disease	1	2	1	2
No data	4	6	–	

Abbreviation: FEC, fluorouacil, epirubicin, and cyclophosphamide.
*For three patients pathologic tumor size was unknown.

Table 9. Planned versus performed type of surgery in patients who received 4 cycles of pre-operative FEC

was already indicated before the administration of chemotherapy. After chemotherapy, the pathologic node-negative rates were 63% and 51%, respectively. This indicates that axillary nodal response to preoperative chemotherapy was actually better in downstaged patients than in the others who underwent breast-conserving surgery. Remarkably, there was an obvious similarity in both clinical tumor size before preoperative chemotherapy and pathologic tumor size between the two groups (Table 9). These differences may well be a result of differences in initial tumor-node-metastasis system classification between both of these patient groups. However, the fact that clinical T and N stages were to a large extent similar does not support this hypothesis. Conclusively, these findings do support the assumption that radical conservative surgery, especially after downstaging, may be more difficult because of the fact that tumor-free margins are more difficult to assess after preoperative chemotherapy.

Quality of Life

Unfortunately, only one institution has collected quality-of-life data on a total number of 20 patients. These data are insufficient to report here or to draw any conclusion on the effect of preoperative chemotherapy on quality of life.

Discussion

In 1986, the Breast Cancer Cooperative Group started a trial to study the effectiveness of one course of fluorouracil, doxorubicin, and cyclophosphamide administered perioperatively within 36 hours after surgery in early breast cancer patients. This regimen resulted in significantly improved locoregional control and disease-free survival rates [10]. Therefore, the logical next step was to start a trial that would study the qualities of preoperative chemotherapy.

EORTC trial 10902 was designed to address whether preoperative chemotherapy yields the same or better results in terms of overall and disease-free survival compared with the same type of chemotherapy administered postoperatively and whether preoperative chemotherapy allows more breast-conserving therapies. A third objective was to assess the value of tumor response to preoperative chemotherapy as a predictor of disease outcome. Several randomized, clinical, phase III trials that compared postoperative adjuvant chemotherapy and preoperative chemotherapy were performed in the past two and a half decades. These trials have been listed in Tables 10 to 12. A comparison of the results of these trials is difficult because of the fact that the study protocols differ substantially in design and chemotherapeutic regimen. However, to date none of these trials, including EORTC trial 10902, has been able to show a positive effect of preoperative chemotherapy in terms of progression-free or overall survival.

Two trials, conducted by Mauriac and Scholl [15-20] initially reported a significant positive effect of preoperative chemotherapy on progression-free and overall survival, but after a longer period of follow-up, the significant benefit of preoperative chemotherapy on survival had disappeared. In addition, in the Mauriac trial, locoregional control was worse in the preoperative arm compared with the standard arm. Of the trials listed in Tables 10 through 12, the National Surgical Adjuvant Breast and Bowel Project B-18 [21,22] trial is similar in terms of study design to the EORTC trial. Fisher et al [21,22] studied the efficacy of four courses of preoperative doxorubicin and cyclophosphamide in 1,523 women with primary operable breast cancer. Contrary to the EORTC trial, the first course of postoperative chemotherapy was not administered directly after surgery. Overall survival, progression-free survival, and recurrence rates were not significantly different between the study and the postoperative population. Interestingly, the authors observed a significantly higher rate of ipsilateral breast recurrences in patients who underwent a lumpectomy as a result of downstaging compared with the rate in patients who underwent a lumpectomy as planned. We observed a similar effect on overall survival in patients who underwent breast-conserving surgery as a result of downstaging. However, we did not find such an effect on locoregional recurrence rates. Nevertheless, these results demonstrate an important potential danger induced by tumor downstaging. Even if clinical assessment of tumor response demonstrates tumor shrinkage as a result of chemotherapy, there is no absolute proof that the tumor has actually shrunken in size. Several authors demonstrated a loss of density in tumors treated by chemotherapy but no shrinkage [23-25]. In our trial, the mammographies before and after preoperative chemotherapy of 83 patients were revised and correlated with histologic data, and a similar effect on the assessment of tumor response was found (data not shown). Thus, treating downstaged tumors with more breast-conserving modalities may result in a higher false-negative rate of tumor-negative surgical margins. In the B18 trial, a clinical overall response was seen in 79%, whereas 35% of the preoperative chemotherapy group experienced a cCR. A pCR, however, occurred in only 9% of these patients. Disease-free, relapse-free, distant disease-free, and overall survival were better in women whose tumors showed a pCR compared with those patients with residual disease. This is in accordance with the results from the EORTC 10902 study and the experience of other investigators [19,26].

In the EORTC trial, tumor response to preoperative chemotherapy was low in

Study	No. of Patients	Median Follow-up (months)	Clinical TNM (%)	Diagnosis	Treatment
Ragaz, 1979-1988, phase II	212		Unknown	FNA	I: 1× CMF → Mast/BCT → 8× CMF II: Mast/BCT → 9× CMF
Mauriac, 1985-1989, phase III	272	124	II-IIIa T2: 82 T3: 18 N0: 44	Drill biopsy	I: 3× EVM + 3× MTV → T0; RT/T1; BCT/>T1; Mast II: Mast; if ER−/N+ → 3× EVM + 3× MTV
Semiglazov, 1985-1990, phase III	271	53	IIb-IIIa T1-2: 18 T3: 82 N0: 31	FNA	I: 1-2× TMF + RT → Mast → 4-5× TMF II: RT → Mast → 6× TMF
Scholl, 1986-1990, phase III	414; 390 assessable	105	T2-3 N0-1 T2: 73 T3: 27 N0: 41	Drill biopsy	I: 4-6× FAC → RT ± Mast/BCT (if T ≠ 0) II: RT ± Mast/BCT (if T ≠ 0) → 4× FAC
NSABP B-18, 1988-1993, phase III	1523	60	T1-3 N0-1 T1: 28 T2: 59 T3: 13 N0: 74	FNA	I: 4× AC → Mast/BCT II: Mast/BCT → 4× AC
Makris, Powles, 1990-1995, phase III	309; 293 assessable	48	T1: 12 T2: 82 T3: 5 N0: 81	Trucut biopsy/FNA	I: 4× 3M/2M + TAM → Mast/BCT ± RT → 4× 3M/2M II: Mast/BCT ± RT → 8× 3M/2M + TAM
EORTC 10902, 1991-1999, phase III	698	56	T1c-4b N0-1 T1: 14 T2: 58 T3: 21 T4: 5 N0: 48	Core needle biopsy/FNA	I: 4× FEC → Mast/BCT ± RT II: Mast/BCT → 4× FEC → ± RT

Abbreviations: Mast, mastectomy; RT, radiotherapy; T, tumor; CMF, cyclophosphamide, methotrexate, and fluorouracil; EVM, epirubicin, vincristine, and methotrexate; MTV, mitomycin, thiopeta, and vinblastine; TMF, thiopeta, methotrexate, and fluorouracil; FAC, fluorouracil, doxorubicin, and cyclophosphamide; AC, doxorubicin and cyclophosphamide; 3M/2M, methotrexate, mitoxanthrone, ± mitomycin; Tam, tamoxifen; TNM, tumor-node-metastasis; FNA, fine-needle aspiration.

Table 10. Similar trials

comparison with the response rates described in the literature [15-22,26-36]. Clinical overall tumor responses after four to six cycles of preoperative polychemotherapy range approximately between 65% and 90%. The cCR rates vary between 10% and 30%. However, the pCR rate usually is much lower, resulting in a poor correlation. Controversially, in the EORTC 10902, trial 49% of the patients who received preoperative chemotherapy experienced a clinical overall response as assessed by palpation and 7% of the study-population had a cCR. The remarkable discrepancy between our results and those of other authors is difficult to explain. The vast majority of patients received the chemotherapeutic dose stipulated by the protocol, ie, four courses of FEC containing epirubicin 60 mg/m^2, which means that the regimen was well tolerated. Now, one could argue that total cumulative doses of epirubicin lower than 300 mg/m^2 are suboptimal. However, higher doses of epirubicin in a combined chemotherapy schedule have so far not been demonstrated to be more effective in terms of overall or relapse-free survival in primary operable breast cancer [37-40]. Several studies [23-25] have addressed this discrepancy between cCR and pCR

Study	Clinical Overall Response (%)	cCR (%)	pCR (%)	Initial Type of Surgery (%)
Ragaz, 1979-1988, phase II				
Mauriac, 1985-1989, phase III	NA	I: 33	NA	I: 30 BCT 33 RT alone 37 Mast II: All Mast
Semiglazov, 1985-1990, phase III	I: 72 II: 60 (palpation & mammography)	I: 35 II: 28	I: 29 II: 19	I: All Mast II: All Mast
Scholl, 1986-1990, phase III	I: 82 II: 85	I: 30 II: 41	NA	I: 51 RT alone 31 BCT 18 Mast II: 46 RT alone 32 BCT 23 Mast
NSABP B-18, 1988-1993, phase III	I: 80	I: 36	I: 13	I: 67 BCT 33 Mast II: 60 BCT 40 Mast (P = .002)
Makris, Powles, 1990-1995, phase III	I: 84	I: 22	I: 7 (7 DCIS alone)	I: 90 BCT 10 Mast II: 77 BCT 22 Mast (P < .003)
EORTC 10902, 1991-1999, phase III	I: 49 (palpation & mammography)	I: 7	I: 4	I: 35 BCT 60 Mast II: 22 BCT 74 Mast

Abbreviation: NA, not available.

Table 11. Similar trials

Study	5-Year LRR (%)	5-Year DFS (%)	5-Year DDFS (%)	5-Year OS (%)
Ragaz, 1979-1988, phase II				I: 74 (10 years) II: 73 (10 years) P = .9
Mauriac, 1985-1989, phase III	I: 74 (10 years) II: 91 (10 years) P = ?	NA	Δ NS/NA (10 years)	Δ NS/NA (10 years)
Semiglazov, 1985-1990, phase III	NA	I: 81 II: 72 P < .05	NA	I: 86 II: 78 P > .05
Scholl, 1986-1990, phase III	I: 73 II: 81 Δ NS	I: 59 II: 55 P = .4	I: 73 II: 68 P = .09	I: 65 (10 years) II: 60 (10 years) P = .18
NSABP B-18, 1988-1993, phase III	I: 86 II: 89 P = .23 IBTR	I: 67 II: 67 P = .99	I: 73 II: 73 P = .7	I: 80 II: 80 P = .83
Makris, Powles, 1990-1995, phase III	I: 97 (4 years) II: 96 (4 years) Δ NS	I: 82 (4 years) II: 80 (4 years) P = .8	NA	I: 78 (4 years) II: 78 (4 years) P = 1.0
EORTC 10902, 1991-1999, phase III	I: 89 (4 years) II: 92 (4 years) P = .61 all events	I: 64 (4 years) II: 69 (4 years) P = .27	I: 69 (4 years) II: 72 (4 years) P = .23	I: 81 (4 years) II: 85 (4 years) P = .38

Abbreviations: LRR, time to locoregional recurrence; DFS, disease-free survival; DDFS, distant disease-free survival; OS, overall survival; Δ NS, no significant difference; IBTR, ipsilateral breast tumor recurrence.

Table 12. Similar trials

and compared clinical measurements with mammographic and ultrasonographic measurements. These studies generally demonstrate an overestimation of tumor response by palpation alone. In the majority of clinical trials that study the effects of preoperative chemotherapy, clinical measurements are commonly used to assess the amount of tumor response, as described by the guidelines of the International Union Against Cancer. In EORTC trial 10902, tumor response was measured by using the data of both palpation and mammographic tumor measurements. Unfortunately, we were not able to demonstrate this confounding error induced by using palpation measurements alone because of a poor registration of measurements. Conclusively, mammographic measurements should be implemented in the assessment of tumor response on a standard basis to give an objective idea of the degree of tumor response. Moreover, in the case of a cCR, it may be helpful to perform ultrasonography in selecting those patients who do not require surgery after preoperative chemotherapy and in localizing abnormalities in those who do [41,42].

In locally advanced and primary inoperable breast cancer, the purpose of preoperative treatment is to enable adequate local treatment, favorably leading to breast conservation. In patients with stage I or II breast cancer who are candidates for breast-conserving therapy irrespective of preoperative chemotherapy, the goal of preoperative chemotherapy is unclear. Some investigators argue that tumor response to preoperative chemotherapy is an independent predictor of treatment outcome. Therefore, it could be of benefit for breast cancer patients to adjust systemic adjuvant treatment at an early stage if tumor response to preoperative chemotherapy is inadequate.

Controversially, preoperative chemotherapy might lead to overtreatment of breast cancer patients. This can be explained by the fact that patients receive systemic treatment regardless of histologic staging of the tumor and axillary nodal status. The breast-conserving therapy rate was higher in the preoperative chemotherapy group in comparison with the postoperative chemotherapy group. This finding, together with the equal locoregional control rate in both groups, advocates the advantageous role of primary chemotherapy in breast-conserving management. On the other hand, 14% of patients who initially were supposed to undergo breast-conserving surgery received a modified radical mastectomy. This suggests that a delay in surgical treatment as a result of the use of primary chemotherapy can result in a more aggressive type of surgical management of breast cancer in a considerable number of patients. In addition, a hypothesis-generating analysis that compared survival rates of patients who underwent breast-conserving surgery as a result of downstaging of the tumor with patients who underwent breast-conserving surgery as initially was planned showed a favorable trend for the latter group of patients. Therefore, it can be hypothesized that patient prognosis is determined by the initial tumor stage and not tumor stage after preoperative chemotherapy.

The idea that changes in surgical management after preoperative chemotherapy are solely because of either increase or decrease of tumor volume is arguable. Because preoperative chemotherapeutic regimens take approximately 3 months to complete, patient or doctor surgical preferences may be altered for subjective reasons during this period of time.

The use of preoperative or primary chemotherapy was introduced approximately three decades ago in locally advanced breast cancer. Since then, its role in the

management of locally advanced breast cancer has been firmly established. However, the advantages are not clear in early breast cancer. Despite the fact that preoperative chemotherapy may permit more breast-conserving treatment modalities, there may be problems, for instance in achieving adequate locoregional control as a result of the difficulty of assessing tumor margins after the administration of preoperative chemotherapy.

Moreover, it has become clear that the supposed survival benefits of preoperative chemotherapy based on preclinical data are not exerted in primary operable breast cancer patients. Although benefits of preoperative chemotherapy in early breast cancer patients are less clear compared with the locally advanced breast cancer patients, the potential to enhance breast-conserving therapy makes it an attractive treatment modality. Postmenopausal early breast cancer patients especially might benefit from preoperative chemotherapy, although preoperative chemotherapy may be less beneficial for young breast cancer patients who are at a higher risk of recurrence of disease, especially after primary conservative therapy. Although this trial did not show such differences (data not shown), other investigators have found young age to be a strong independent prognostic factor for recurrence after breast-conserving therapy [11,43,44].

Moreover, the possibility of studying the effects of chemotherapy on well-established tumor characteristics as well as experimental tumor markers makes chemotherapy in the preoperative setting highly attractive for translational research purposes [45]. The comparison of core needle biopsies with the same tumor after systemic treatment is a worthwhile reason to continue preoperative chemotherapy trials in early breast cancer.

Unfortunately, not many data concerning quality-of-life issues in relation to preoperative chemotherapy are available in the literature. Quality-of-life studies, however, have been performed to investigate the effects of breast-conserving therapy versus mastectomy and fail to show a clear benefit for the conservative treatment modality, except for a slightly less impaired body image [46-49]. Considering the fact that preoperative as well as postoperative chemotherapy seems to yield similar results in terms of prognosis, this might be a conclusive factor on the decision of which chemotherapeutic strategy should be chosen. Therefore, the role of preoperative chemotherapy should be studied in future trials that focus on translational research, equivalence, quality of life, and local control, rather than trying to detect overall and progression-free survival differences.

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