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 9

Efficacy of adjuvant chemotherapy according to hormone receptor status in young breast cancer patients

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Abstract

Breast cancer at a young age is associated with an unfavorable prognosis. We studied the effect of adjuvant chemotherapy in young breast cancer patients in relation to hormone receptor status. Paraffin embedded tumor material was collected from 480 early stage breast cancer patients younger than 41 years who participated in one of four EORTC trials. Estrogen receptor- and progesterone receptor status were assessed using immunohistochemistry.. The median follow up period was 7.3 years. Patients that received chemotherapy did not have significant differences in OS (HR 0.87, P = 0.63) and DMFS (HR 1.36, P = 0.23) rates according to ER status. Patients with ER-positive tumors who did not receive adjuvant chemotherapy had better OS (HR 0.41, P < 0.01) and DMFS (HR 0.59, P = 0.02) rates than those with ER-negative tumors. Patients with ER-positive tumors benefit less from adjuvant systemic chemotherapy than patients with ER-negative tumors. These differences were similar for PgR status. In conclusion, young patients with ER positive tumors seem to benefit less from adjuvant systemic chemotherapy than patients with ER negative tumors.

Introduction

Breast cancer in premenopausal women is associated with worse outcome compared to postmenopausal patients [1]. Approximately 7% of women diagnosed with breast cancer are aged below 40 years [2]. Especially very young women, i.e. < 35 years are at a high risk of developing distant metastases and therefore are recommended to receive adjuvant systemic chemotherapy regardless of tumor stage [3]. In addition, high local regional recurrence rates after breast conserving therapy have been reported in young premenopausal breast cancer patients [4]. Although it is clear that young age is an independent prognosticator of adverse outcome in breast cancer, controversies exist regarding the optimal treatment in this population.
Adjuvant systemic chemotherapy in premenopausal patients has been shown to improve survival [5], but controversy still exists about the role of chemotherapy in hormone receptor positive patients. Since chemotherapy alone in estrogen receptor (ER) and/or progesterone receptor (PgR)- positive breast cancer patients may not be sufficient [6], several trials in premenopausal ER and/or PgR- positive breast cancer patients have studied the role of ovarian ablation using LHRH-analogues [7,8,9,10]. One study by Aebi et al. [6] very clearly showed that the endocrine effects of chemotherapy alone might not be sufficient for very young breast cancer patients. In this study, it was shown that estrogen receptor positive tumors in patients younger than 35 years and treated with CMF had a significantly worse disease-free survival compared to estrogen receptor negative patients.
To detect whether we could confirm these data by finding similar results, we studied the efficacy of chemotherapy in young breast cancer patients according to estrogen receptor and progesterone receptor status, we selected patients younger than or equal to 40 years of age at time of primary diagnosis from 4 European Organization for Research and Treatment of Cancer (EORTC) trials, 10801, 10854, 10902, and 22881, that were conducted by the EORTC Breast Cancer- and Radiotherapy Group.

Patients and Methods

Data was collected from four EORTC trials. In total, 9938 patients participated in these trials and 934 of these patients were younger or equal to 40 years of age at time of diagnosis. The trial designs are summarized below:

EORTC trial 10801 (1980-1986, median follow up 13.4 years) was conducted in order to assess the safety of breast conserving treatment. In this trial, patients were randomized between breast conserving surgery combined with radiotherapy and radical mastectomy. Six cycles of adjuvant chemotherapy with cyclophosphamide 100 mg/m^2 given orally on days 1-14, methotrexate 40mg/m^2 given intravenously on days 1 and 8, and 5-fluorouracil 600 mg/m^2 given intravenously on days 1 and 8, were indicated for all patients under the age of 55 with positive nodes. In this study, 902 patients were randomized [11].

EORTC trial 10854 (1986-1991, median follow up 10.8 years) studied the question whether one course of peri-operative chemotherapy given directly after surgery yields better results in terms of treatment outcome than surgery alone. Peri-operative chemotherapy consisted of one single course of doxorubicin 50 mg/m^2, 5-fluorouracil 600 mg/m^2, and cyclophosphamide 600 mg/m^2 (FAC), administered intravenously within 36 hours after surgery. For axillary lymph node-positive premenopausal patients in the peri-operative chemotherapy group adjuvant chemotherapy consisting of 5 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) was recommended. For node-positive patients younger than 50 years who did not receive peri-operative chemotherapy, one conventional course of FAC followed by five cycles of CMF after surgery was recommended. Postmenopausal patients were recommended to receive tamoxifen. 2795 patients were included in this trial [12].

EORTC trial 10902 (1991-1999, median follow up 6.1 years) was set up to determine the value of pre-operative chemotherapy. Patients were randomized to receive four cycles of chemotherapy either before or after surgery. Chemotherapy consisted of four cycles of 5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, and cyclophosphamide 600 mg/m^2 (FEC) administered intravenously, at 3-weekly intervals. In the pre-operative chemotherapy group, surgical therapy followed within four weeks of the fourth course of chemotherapy. In the postoperative chemotherapy group, the first cycle was given within 36 hours after surgery. Patients $\geq$ 50 years received tamoxifen for 2 years. A total number of 698 patients were randomized [13].

EORTC trial 22881 enrolled 5569 patients between 1989 and 1996. Stage I/ II breast cancer patients were randomized between to undergo 50 Gy irradiation of the whole breast with or without an additional dose of 16 Gy to the tumor bed after lumpectomy. Patients with a microscopically incomplete resection were assigned to receive a boost dose of 10 Gy or 26 Gy. Premenopausal patients with axillary lymph node involvement received chemotherapy and postmenopausal patients received tamoxifen [14].

In all trials if adjuvant chemotherapy was indicated, patients either received CMF or

Number of patients	N	480
Clinical tumor size	cT1	185
	cT2	276
	cT3	17
	missing data	2
Histological tumor size	pT1	292
	pT2/3	151
	missing data	37
Nodal status	N –	288
	N +	188
	missing data	4
Surgery	BCS*	393
	Mastectomy	86
	missing data	1
Adjuvant chemotherapy	No	279
	Yes	200
	missing data	1
Tamoxifen**	No	273
	Yes	9
	missing data	198
Histological grade	I	70
	II	145
	III	255
	missing data	10
Estrogen receptor	+	288
	-	180
	missing data	12
Progesterone receptor	+	223
	-	241
	missing data	16

* Breast Conserving Surgery
** During the period of time in which these trials were conducted, tamoxifen was not routinely given to premenopausal ER-positive patients

Table 1. Patient & Tumor characteristics

an anthracyclin-based regimen (FAC or FEC). Adjuvant hormonal therapy for premenopausal hormone receptor positive patients was not yet recommend at the time when these trials were conducted. In the oldest two trials tamoxifen administration was not even recorded. This explains the high number of patients for which no information was found on tamoxifen use. In the trials where tamoxifen use was recorded, less than 5% of patients ≤ 41 years received tamoxifen.

ER staining and PgR staining
Paraffin embedded tumor material was collected from 549 patients ≤ 40 years. Tumors were histologically graded using H&E slides as described previously [15].
Immunohistochemical staining for estrogen receptor and progesterone receptor status was performed using a tissue micro array [16,17,18,19]. Three core biopsies were taken from each tumor block and inserted into a donor block. Immuohisto-chemical staining for estrogen receptor was performed using the monoclonal antibody DAKO-ER, 1D5 (Dakopatts, Glostrup, Danmark); for progesterone receptor using the monoclonal antibody mPRI (TRANSBIO, Paris, France. Immunohistochemical staining was scored using a semiquantative system based on the percentage of positive nuclei. After counting the percentage of positive nuclei in three core biopsies the mean value was taken. For estrogen- and progesterone receptor, tumors with >10% of the tumor cells showing nuclear staining were considered positive.

Statistical analysis
Analyses were performed for distant metastasis-free survival (DMFS) and overall survival (OS). Distant metastasis-free survival was defined as the interval from time of randomization until time of distant metastasis or death, whichever event came first. Overall survival was defined as time from randomization to death from any cause. Survival curves were estimated using the Kaplan-Meier method [20]. Differences in survival were analysed using Cox proportional hazard models [21]. All statistical analyses were performed using SPSS software. A direct comparison of patients who received chemotherapy versus patients who did not receive chemotherapy per hormone receptor status group was not feasible since this would

	No adjuvant chemotherapy N = 279	Adjuvant chemotherapy N = 200
ER +	161	126
ER -	110	70
PgR +	135	88
PgR -	135	105
T1	187	105
T2 / T3	76	75
N –	259	29
N +	18	170
BCT	247	146
Mastectomy	32	53

*Missing data not shown

Table 2. Patient characteristics specified by adjuvant chemotherapy*

	No adjuvant chemotherapy	Adjuvant chemotherapy
Deaths (N = 102)		
ER +	19	35
ER -	29	19
Distant metastasis or death (N = 150)		
ER +	37	54
ER -	38	21

Table 3. Type of events

introduce a selection bias in this retrospective analysis. This due to the fact that the vast majority of patients receiving chemotherapy had positive axillary lymph nodes. Therefore, conclusions in this explorative analysis were based upon indirect comparisons.

Results

Paraffin embedded tumor specimens were collected for 480 patients ≤ 40 years at time of diagnosis. Patient characteristics are listed in Table 1. For 12 patients, ER status could not be scored and for 16 patients PgR status could not be scored. 288 patients were deemed ER positive whereas 223 patients were PgR positive. Two hundred patients received prolonged adjuvant systemic chemotherapy and 279 patients did not receive adjuvant systemic chemotherapy. Ninety-four percent of patients that did not receive chemotherapy were node-negative and eighty-five percent of patients that did receive chemotherapy were node-positive. Characteristics related to adjuvant systemic chemotherapy treatment are listed in Table 2.
At time of the analysis, 102 patients had died and 150 patients developed a distant recurrence or died. The number of events stratified by estrogen receptor status is listed in Table 3. The median-follow-up period at time of analysis was 7,3 years. Overall, patients with ER-positive tumors had better OS rates compared to ER-negative patients, (HR 0.63, 95%CI 0.43 - 0.93, P= 0.02, Figure 1). Survival rates after a median follow up of 7 years were approximately 82% for the ER positive group and 77% for the ER negative group. DMFS rates were 70% and 66% respectively which was not statistically significant (HR 0.90, 95% CI 0.65 - 1.24, P = 0.51, Figure 2).
Progesterone receptor status yielded similar results in terms of overall survival and distant metastasis-free survival. Patients with progesterone positive tumors had better OS (HR 0.59, 95%CI 0.4 - 0.88, P = 0.01) but for DMFS this difference was not of statistical significance (HR 0.78, 95%CI 0.57 - 1.01, P = 0.14).

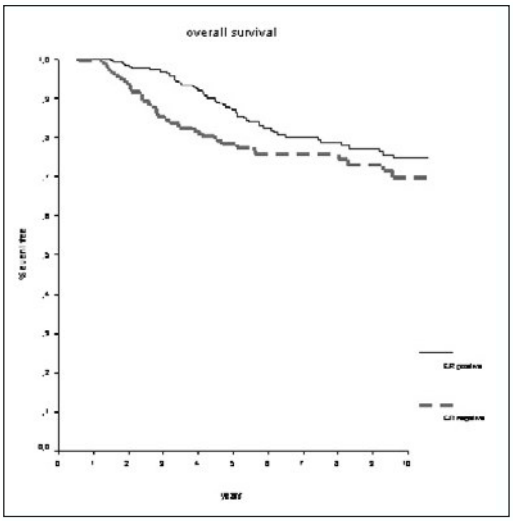

Figure 1. Overall survival for all patients

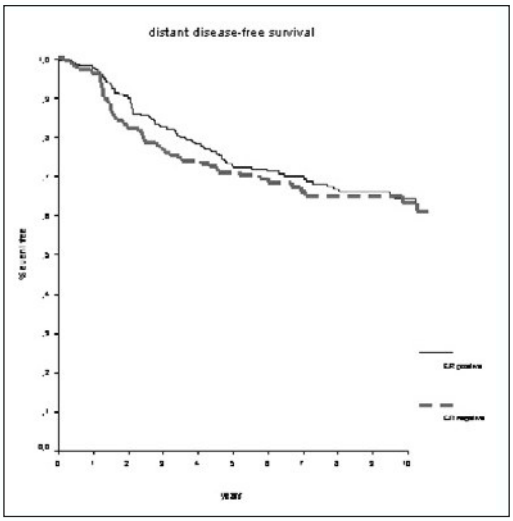

Figure 2. Distant metastasis-free survival for all patients

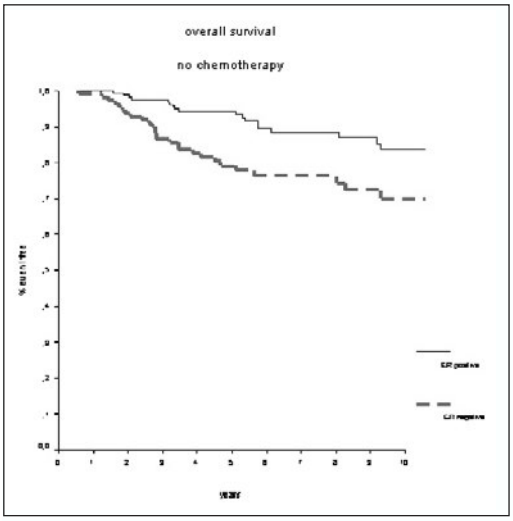

Figure 3. Overall survival in patients who did not receive adjuvant chemotherapy

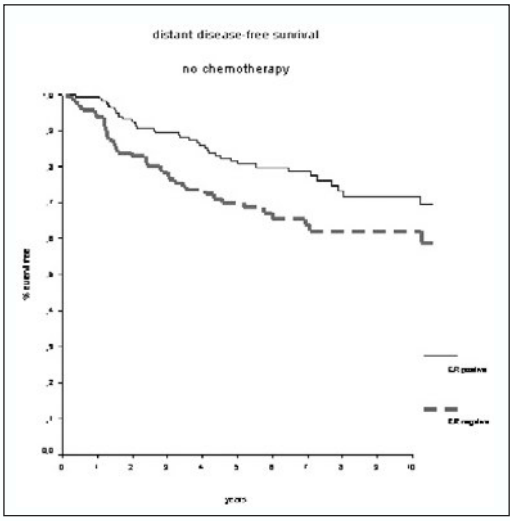

Figure 4. Distant metastasis-free survival in patients who did not receive adjuvant chemotherapy

Patients that did not receive prolonged adjuvant chemotherapy

Estrogen receptor status

In the subset of patients that did not receive adjuvant systemic chemotherapy, positive ER status was associated with better OS (HR 0.41, 95%CI 0.23 - 0.74, P < 0.01, figure 3). Survival rates at 7 years were 90% for the ER positive group and 77% for the

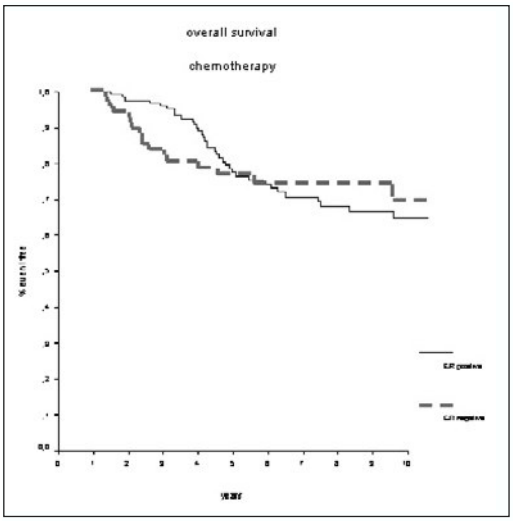

Figure 5. Overall survival in patients who received adjuvant chemotherapy

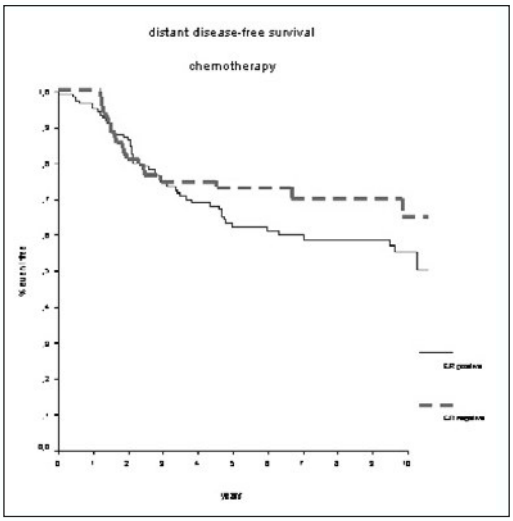

Figure 6. Distant metastasis-free survival in patients who received adjuvant chemotherapy

ER negative group. DMFS rates in the subset of patients that did not receive adjuvant systemic chemotherapy were significantly better for ER positive patients as well, 80% and 64% respectively (HR 0.59, 95%CI 0.37 - 0.92, P = 0.02, figure 4).

Progesterone receptor status
PgR positive patients who did not receive adjuvant chemotherapy had better OS (HR 0.44, 95%CI 0.24 - 0.8, P < 0.01). OS rates were 88% and 75% for ER positive and ER negative patients. DMFS rates were 79% for PgR positive patients and 67% for PgR negative patients respectively. However, this difference did not reach statistical significance (HR 0.66, 95%CI 0.42 - 1.04, P = 0.07).

Patients who received prolonged adjuvant systemic chemotherapy

Estrogen receptor status
In the group of two hundred patients that did receive adjuvant systemic chemotherapy treatment outcome was not significantly different between ER positive- and ER negative breast cancer patients. OS rates were 70% for the ER positive group and 75% for the ER negative group (HR 0.87, 95%CI 0.50 - 1.52, P = 0.63, figure 5) and DMFS rates were 59% for the ER positive group and 70% for the ER negative group (HR 1.36, 95% CI 0.82 - 2.26, P = 0.23, figure 6).

Progesterone receptor status
Patients who had PgR negative tumors and received adjuvant systemic chemotherapy did not have significant differences in terms of OS and DMFS rates. Both in the PgR positive and PgR negative patient group, OS was 72% at 7 years of follow up (HR 0.84, 95%CI 0.49 - 1.43, P = 0.51). DMFS did not differ significantly between PgR positive

patients and PgR negative patients who received adjuvant chemotherapy. DMFS rates were 59% for the PgR positive group and 64% for the ER negative group (HR1.02, 95%CI 0.65 - 1.6, P = 0.93).

Multivariate analysis

Multivariate Cox regression overall survival analyses were performed for ER status and PgR status separately. Other covariates included nodal status, tumor size, and the administration of prolonged adjuvant chemotherapy. Both ER status (RR 1.65) and PgR (1.56, data not shown) status remained independent prognostic factors with a significant impact on overall survival (Table 4).

Discussion

Adjuvant systemic chemotherapy is a well-established treatment modality in premenopausal breast cancer. In patients younger or equal to 35 years, chemotherapy is advocated regardless of nodal status and tumor size and grade [3]. However, several reports have questioned the efficacy of chemotherapy in premenopausal patients with ER-positive breast cancer [6,7,10].
We demonstrated that ER–positive and/or PgR positive patients ≤ 40 years who received prolonged adjuvant chemotherapy showed no advantage in treatment outcome compared with ER-/PgR-negative patients, whereas ER-/PgR- positive patients who did not receive adjuvant chemotherapy had better overall survival rates compared with their ER-/PgR- negative counterparts. In terms of survival, figure 5 even suggests that the proportional hazards assumption is not justified in the assessment of the effect of chemotherapy according to hormone receptor status. Therefore we conclude that treatment efficacy of adjuvant chemotherapy is less in young hormone receptor positive patients compared to young hormone receptor negative patients. We did not perform direct comparisons between patients who received chemotherapy versus patients who did not receive chemotherapy according to hormone receptor status. Axillary lymph node status would have induced a confounding error and since the majority of patients that did receive chemotherapy also had positive axillary lymph nodes. Hormone receptor status therefore, may not have been of significant impact on outcome in this subgroup.
However, in the multivariate analysis including ER status, axillary lymph node status, tumor size and the administration of prolonged adjuvant chemotherapy, ER status remained an independent prognostic factor for overall survival (RR1.65, 95%CI 1.09 - 2.5 P = 0.02, Table 4). Since these patients participated in trials in which adjuvant tamoxifen was not routinely given to hormone receptor positive premenopausal patients, less than 5% of the study population received tamoxifen, the effect of adjuvant tamoxifen could not be measured.
Similar findings were recorded if ER status was replaced by PgR status (RR 1.56, 95%CI 1.02 - 2.39, P = 0.04).
We realize that this is a retrospective analysis using heterogeneous data from different randomized trials and therefore any conclusions have to be drawn with

Overall survival			
	RR	95% CI	P – value
ER negative	1.65	1.09 – 2.5	0.02
pN+	1.7	0.79 – 3.66	0.17
pT2/3	1.66	1.09 – 2.52	0.02
Adjuvant chemotherapy	1.02	0.48 – 2.17	0.96

Table 4. Multivariate Cox overall survival regression analysis

caution. Preferably, we should have liked to compare chemotherapy versus not in hormone receptor positive patients and then compare chemotherapy versus not in hormone receptor negative patients. However, since this is not a randomized comparison, the confounding effect of axillary lymph node status would have induced a significant selection bias. On the other hand, our findings are in accordance with data from Aebi et al. [6] who demonstrated that young premenopausal breast cancer patients treated with adjuvant CMF chemotherapy had a higher risk of relapse and death than older premenopausal patients, especially if their tumors were ER-positive. In this study, ER was assessed using a ligand-binding assay; in our study ER has been assessed using immunohistochemistry. By analyzing ER status centrally, we have provided standardized ER measurements for all tumors in the study.

In order to optimize adjuvant systemic treatment in premenopausal breast cancer patients, several investigators have studied the role of ovarian suppression by LHRH agonists.

The Zoladex‰ Early Breast Cancer Research Association (Zebra) trial [7,8] compared goserelin and CMF in1640 node-positive, premenopausal and perimenopausal patients, aged 50 years or less, with early breast cancer. After a median follow-up of 6 years, goserelin and CMF showed equivalent disease-free survival rates in ER positive patients (HR 1.01, 95%CI 0.84 - 1.20). However in the ER negative subgroup, a significant advantage in favor of CMF was found (HR 1.76, 95%CI 1.27 - 2.44). A recent update of the analysis demonstrated similar results. In addition, patients who received LHRH agonists suffered less from treatment related side effects than patients who received chemotherapy [22].

Other trials studying the effect of goserelin with or without tamoxifen versus CMF in premenopausal hormone receptor positive breast cancer patients also demonstrate equivalent or even better disease-free survival rates but this has not yet resulted in better overall survival rates [23,24].

Although these results underline the fact that chemotherapy may be equivalent to hormonal ovarian suppression in terms of treatment outcome in ER positive patients, these results fail to demonstrate a superior effect of LHRH agonists over adjuvant chemotherapy.

In conclusion, we have demonstrated in a subset of patients aged 40 years or less at time of diagnosis that hormone receptor status is an independent prognostic factor on distant metastasis-free survival and overall survival. Moreover, we showed that hormone receptor status influences response to chemotherapy. Therefore, we can conclude that chemotherapy alone is not sufficient hormone receptor positive young breast cancer patients.

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