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Premenopausal endocrine-responsive early breast cancer: who receives chemotherapy?

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Background: The role of chemotherapy in addition to combined endocrine therapy for premenopausal women with endocrine-responsive early breast cancer remains an open question, yet trials designed to answer it have repeatedly failed to adequately accrue. The International Breast Cancer Study Group initiated two concurrent trials in this population: in Premenopausal Endocrine Responsive Chemotherapy (PERCHE), chemotherapy use is determined by randomization and in Tamoxifen and Exemestane Trial (TEXT) by physician choice. PERCHE closed with inadequate accrual; TEXT accrued rapidly.

Methods: From 2003 to 2006, 1317 patients (890 with baseline data) were randomly assigned to receive ovarian function suppression (OFS) plus tamoxifen or OFS plus exemestane for 5 years in TEXT. We explore patient-related factors according to whether or not chemotherapy was given using descriptive statistics and classification and regression trees.

Results: Adjuvant chemotherapy was chosen for 64% of patients. Lymph node status was the predominant determinant of chemotherapy use (88% of node positive treated versus 46% of node negative). Geography, patient age, tumor size and grade were also determinants, but degree of receptor positivity and human epidermal growth factor receptor 2 status were not.

Conclusions: The perceived estimation of increased risk of relapse is the primary determinant for using chemotherapy despite uncertainties regarding the degree of benefit it offers when added to combined endocrine therapy in this population.

Key words: chemotherapy, estrogen receptor, exemestane, ovarian ablation, premenopausal, tamoxifen

introduction

Chemotherapy, tamoxifen and ovarian function suppression/ablation (OFS) are individually effective adjuvant treatments for women <50 years of age with estrogen receptor (ER)-positive breast cancer, as shown in several individual trials and confirmed by meta-analyses [1–5]. For patients with endocrine-nonresponsive disease, the effect of adjuvant chemotherapy is independent of endocrine mechanisms [6, 7]. However, for endocrine-responsive [i.e. ER- and/or progesterone receptor (PgR)-positive] breast cancer the benefit of chemotherapy is due to a complex mixture of cytotoxic and endocrine mechanisms. The additional benefit of chemotherapy for premenopausal patients with endocrine-responsive breast cancer who receive combined endocrine treatment with OFS and tamoxifen (or an aromatase inhibitor) remains an open question that prospective randomized clinical trials have been unsuccessful in answering, as diverging opinions regarding its efficacy result in some physicians recommending it while others do not [8].

In 1993, the International Breast Cancer Study Group (IBCSG) activated a randomized clinical trial (IBCSG 11-93) to investigate the role of adjuvant chemotherapy in premenopausal patients with node-positive (N+), hormone receptor-positive invasive breast cancer who receive combined endocrine therapy with OFS and tamoxifen (Figure 1A) [9, 10].

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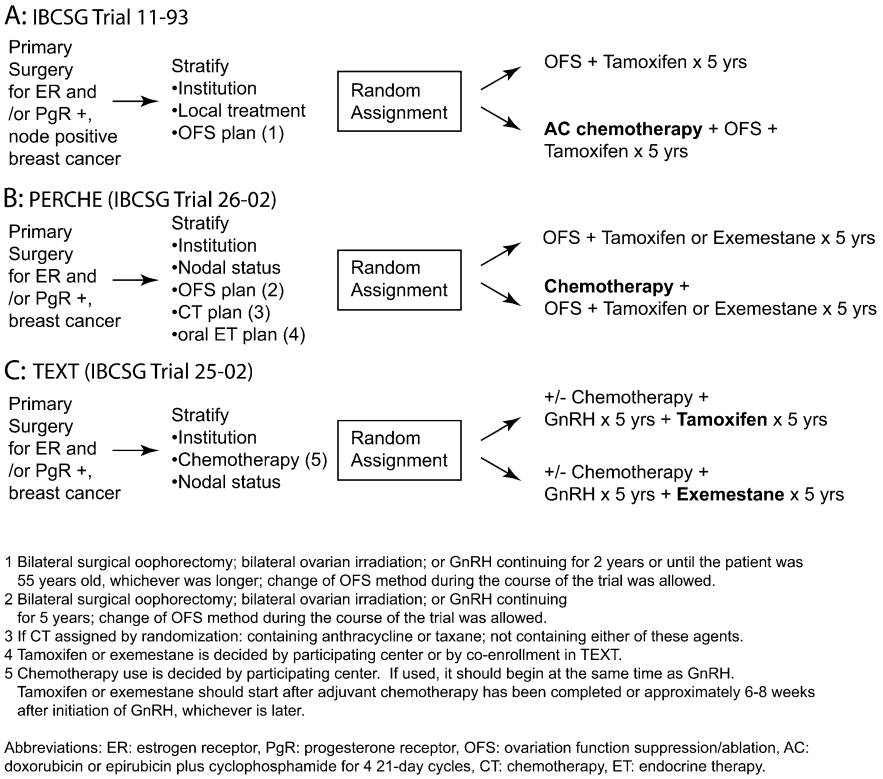


1 Bilateral surgical oophorectomy; bilateral ovarian irradiation; or GnRH continuing for 2 years or until the patient was 55 years old, whichever was longer; change of OFS method during the course of the trial was allowed.
2 Bilateral surgical oophorectomy; bilateral ovarian irradiation; or GnRH continuing for 5 years; change of OFS method during the course of the trial was allowed.
3 If CT assigned by randomization: containing anthracycline or taxane; not containing either of these agents.
4 Tamoxifen or exemestane is decided by participating center or by co-enrollment in TEXT.
5 Chemotherapy use is decided by participating center. If used, it should begin at the same time as GnRH. Tamoxifen or exemestane should start after adjuvant chemotherapy has been completed or approximately 6-8 weeks after initiation of GnRH, whichever is later.

Abbreviations: ER: estrogen receptor, PgR: progesterone receptor, OFS: ovariation function suppression/ablation, AC: doxorubicin or epirubicin plus cyclophosphamide for 4 21-day cycles, CT: chemotherapy, ET: endocrine therapy.

Figure 1. Trial designs for (A) International Breast Cancer Study Group (IBCSG) Trial 11-93, (B) Premenopausal Endocrine Responsive Chemotherapy (PERCHE) trial and (C) Tamoxifen and Exemestane Trial (TEXT). All three trials are for premenopausal women with endocrine-responsive [estrogen receptor (ER) and/or progesterone receptor (PgR) -positive] early breast cancer. Trial 11-93 was restricted to patients with node-positive disease.

Patients were randomly allocated to receive four cycles of adjuvant anthracycline-based chemotherapy plus long-term OFS and 5 years of tamoxifen (initiated after chemotherapy) or to receive the same combined endocrine therapy without chemotherapy. From May 1993 to November 1998, 174 patients were randomized and the trial closed prematurely because of the low accrual rate. Patients (median age 45 years) tended to be at intermediate risk according to the St Gallen Consensus Criteria [11], with 97% of patients having one to three nodes involved. After a median follow-up of 10 years, 20 of the 89 patients randomized to chemotherapy plus OFS/tamoxifen and 20 of 85 randomized to OFS/tamoxifen without chemotherapy had relapsed; 12 patients had died of cancer in each group. The estimated 10-year disease-free survival was 73% $\pm$ 5% for both groups (Hazard ratio = 1.02 for addition of AC doxorubicin or epirubicin plus cyclophosphamide for 4 21-day cycles; 95% CI 0.57–1.83; $P = 0.94$) [10]. This trial, although clearly underpowered, raises the question of whether chemotherapy is needed in this intermediate-risk population that received combined endocrine treatment [8].

In 2003, the IBCSG initiated a suite of three complementary tailored treatment investigations, the Suppression of Ovarian Function Trial (SOFT), Tamoxifen and Exemestane Trial (TEXT) and Premenopausal Endocrine Responsive Chemotherapy (PERCHE) trial, designed to answer questions concerning adjuvant treatment for premenopausal women with endocrine-responsive early breast cancer [12, 13]. The TEXT and the PERCHE trials address two questions for women who receive OFS from the start of adjuvant therapy. TEXT (Figure 1C) investigates the role of aromatase inhibitors compared with tamoxifen, and PERCHE (Figure 1B) the value of adding chemotherapy to combined endocrine therapy. These trials involve worldwide participation through the Breast International Group (BIG) network and The Breast Cancer Intergroup of North America.

In PERCHE, whether or not to use adjuvant chemotherapy was determined by random assignment, whereas the oral endocrine agent (tamoxifen or exemestane) combined with OFS was determined by the participating center or by co-enrollment in TEXT. The PERCHE trial had broader eligibility criteria than its predecessor trial IBCSG 11-93 by including patients with node-negative (N−) disease and allowing centers to choose the chemotherapy regimen. Yet from August 2003 to December 2006—at which point the trial was prematurely closed to accrual—only 29 patients were enrolled in PERCHE from 11 centers in seven countries (Australia, Canada, Germany, Hungary, Italy, New Zealand, Switzerland), even though there was widespread consensus among opinion leaders that this was a pivotal study to prospectively determine the role of chemotherapy in patients selected on the basis of clinical criteria. Patients' median age was 46 years (range 36–54 years). Most patients had intermediate risk disease according to the St Gallen Consensus Criteria [11], and had ER-positive and PgR-positive tumors. Patients were equally divided as lymph

N− and N+ disease, with all N+ having one to three positive nodes. Twenty-five of 29 patients were co-enrolled in TEXT.

TEXT has identical eligibility criteria to PERCHE, but the trials have accrued at very different rates. PERCHE, which randomly assigned whether or not to give chemotherapy, accrued on average less than one patient per month. TEXT, which randomly assigned the oral endocrine agent with the center choosing whether to give chemotherapy for individual patients, accrued >40 patients per month. It appears that centers, generally physicians and possibly the patients as well, prefer to make the decision of whether a patient will receive chemotherapy and are unwilling to leave it to chance, but are willing to let chance decide which oral endocrine agent to use. The patients entered in TEXT provide an opportunity to investigate what factors are used in the decision-making process of whether or not to give chemotherapy in addition to combined endocrine therapy in this patient population.

patients and methods

study design

TEXT (IBCSG 25-02) opened for accrual in August 2003 and was designed to enroll 1845 premenopausal women with endocrine-responsive early breast cancer (Figure 1C) who were randomly assigned to receive OFS plus either tamoxifen (20 mg/day) or exemestane (25 mg/day) for 5 years. OFS could be achieved by gonadotropin-releasing hormone (GnRH) analogue (triptorelin 3.75 mg by intramuscular injection every 28 days) until 5 years from randomization; bilateral surgical oophorectomy or bilateral ovarian irradiation was allowed as an alternative after at least 6 months of GnRH analogue. Randomization was stratified by whether or not chemotherapy was planned. The chemotherapy regimen was the center's choice but a planned duration of ≥2 months was recommended if an anthracycline was included or ≥4 months if no anthracycline was given. Patients receiving chemotherapy commenced it after randomization, concurrently with the GnRH analogue. Tamoxifen/exemestane started after adjuvant chemotherapy was completed, if given, or ∼6–8 weeks after the initiation of GnRH analogue, whichever was later.

The study required that randomization be within 12 weeks after definitive surgery for histologically proven invasive breast cancer with steroid hormone receptor-positive tumors, defined as ER and/or PgR expression ≥10% of tumor cells by immunohistochemistry.

From 1 November 2003 to 31 December 2006—the period PERCHE was also open to enrollment—1317 patients were enrolled in TEXT. The analysis cohort was comprised of the 890 (68%) patients with complete baseline case report forms in the database as of April 2007, and excluded the 25 patients who were co-enrolled in both TEXT and PERCHE. For both trials, ethical boards of each participating center approved the protocols and all patients provided written informed consent.

data and statistical considerations

Factors of interest included geographic region (cooperative group network and country, with the United States divided into four census regions), patient age, local–regional treatment plan (type of definitive surgery and whether or not radiotherapy was planned) and locally assessed disease characteristics [steroid hormone receptor status (negative for ER or PgR versus positive for both), percentage of cells staining for ER and PgR (among patients treated at institutions reporting this information), axillary lymph node status (negative or positive as well as number of positive nodes), tumor grade, tumor size, presence of peritumoral vascular invasion (PVI) and human epidermal growth factor receptor 2 (HER2) status of the tumor (considered as HER2 positive if amplified by FISH or 3+ by immunohistochemistry and FISH not done)]. Patients were classified into risk categories according to the 2005 St Gallen Consensus Criteria [11], which consider patient age, number of positive lymph nodes, PVI and tumor size, grade and HER2 status.

Descriptive statistics were presented, either as number and percent of patients or as median, interquartile range (IQR) and range of values. Classification and regression tree (CART) analysis [14] examined which combination of factors best classified whether or not chemotherapy was chosen, and investigated combinations of factors that identified groups of patients in which a small or large proportion received chemotherapy. The initial analysis included geographic region, patient age and disease characteristics; a secondary analysis also included levels of hormone receptor expression among the subset of patients with this information available.

results

Among the population of premenopausal patients with endocrine-responsive disease who were enrolled in TEXT and would be receiving 5 years of combined endocrine therapy, additional adjuvant chemotherapy was chosen for 813 of 1317 (62%) patients. Among the subset of 890 in the study cohort, adjuvant chemotherapy was chosen for 569 (64%).

geography

Overall there was no substantial difference in the percentage of patients in the chemotherapy stratum for BIG centers compared with North American centers (62% versus 66%, respectively) (Table 1). Chemotherapy was consistently given more often to patients with lymph node-positive (N+) disease regardless of geographic region. The proportions of patients receiving chemotherapy, however, varied widely according to region, ranging from 64% to 100% of those with N+ disease and from 18% to 83% of those with lymph node-negative (N−) disease. Among patients with N− disease, only 31% from European centers received chemotherapy compared with 52% from North American centers.

patient age and local–regional treatment

Younger patients were more likely to receive chemotherapy overall and in both lymph node status cohorts (Table 1). The majority of patients who were treated with mastectomy plus radiation therapy received chemotherapy.

disease

Chemotherapy was chosen for 88% of patients with N+ disease compared with 46% with N− disease. The proportion of patients given chemotherapy increased as the number of positive nodes increased, with nearly all patients having four or more positive nodes receiving chemotherapy (Table 2). A clear pattern emerged of choosing chemotherapy according to the 2005 St Gallen risk categories (Table 3) (19% versus 63% versus 96% of low- versus intermediate- versus high-risk patients, respectively), yet the continued role of nodal status within the intermediate category is also apparent (51% of

Table 1. Chemotherapy use by geographic region, patient age and local–regional treatment plan, overall and according to patients' lymph node status

	Lymph node negative		Lymph node positive		All patients		Total
	No adj. CT	Adj. CT	No adj. CT	Adj. CT	No adj. CT	Adj. CT	
All patients	273 (54)	230 (46)	48 (12)	339 (88)	321 (36)	569 (64)	890
Geographical region[a]							
BIG	144 (61)	93 (39)	38 (16)	204 (84)	182 (38)	297 (62)	479
Belgium (2)	6	3	1	4	7	7	14
Germany (2)	3	2	0	1	3	3	6
Hungary (1)	12 (41)	17 (59)	4 (7)	52 (93)	16 (19)	69 (81)	85
Italy (10)	81 (74)	29 (26)	21 (27)	58 (73)	102 (54)	87 (46)	189
Slovenia (1)	4	0	0	1	4	1	5
Sweden (1)	0	0	0	2	0	2	2
Switzerland (8)	18 (82)	4 (18)	8 (36)	14 (64)	26 (59)	18 (41)	44
South Africa (1)	4	0	0	0	4	0	4
Peru (1)	2 (17)	10 (83)	1 (4)	27 (96)	3 (8)	37 (93)	40
Australia/New Zealand (17)	14 (33)	28 (67)	3 (6)	45 (94)	17 (19)	73 (81)	90
North American Intergroup	129 (48)	137 (52)	10 (7)	135 (93)	139 (34)	272 (66)	411
Canada (7)	22 (34)	43 (66)	0 (0)	41 (100)	22 (21)	84 (79)	106
United States (76)	107 (53)	94 (47)	10 (10)	94 (90)	117 (38)	188 (62)	305
Midwest (24)	47 (58)	34 (42)	1 (5)	19 (95)	48 (48)	53 (52)	101
Northeast (20)	27 (51)	26 (49)	4 (10)	38 (90)	31 (33)	64 (67)	95
South (18)	19 (45)	23 (55)	4 (13)	27 (87)	23 (32)	50 (68)	73
West (14)	14 (56)	11 (44)	1 (9)	10 (91)	15 (42)	21 (58)	36
Patient age (years)							
Median [IQR]	45 [41–47]	43 [39–46]	46 [42–48]	42 [38–46]	45 [41–47]	43 [39–46]	43 [39–47]
<35	13 (33)	26 (67)	2 (5)	36 (95)	15 (19)	62 (81)	77
35–39	35 (51)	33 (49)	4 (5)	74 (95)	39 (27)	107 (73)	146
40–44	86 (50)	87 (50)	14 (11)	118 (89)	100 (33)	205 (67)	305
45–49	105 (60)	70 (40)	21 (18)	94 (82)	126 (43)	164 (57)	290
≥50	34 (71)	14 (29)	7 (29)	17 (71)	41 (57)	31 (43)	72
Local–regional treatment[b]							
Mastectomy, no RT	65 (53)	57 (47)	15 (15)	83 (85)	80 (36)	140 (64)	220
Mastectomy, with RT	5 (14)	32 (86)	3 (3)	96 (97)	8 (6)	128 (94)	136
LTM with RT	203 (59)	141 (41)	30 (16)	160 (84)	233 (44)	301 (56)	534

Number (%) unless otherwise specified. Percentages sum across the row and are not provided for small numbers.

[a]Number of centers within the country or region that have randomized patients are given in parenthesis.

[b]Radiation therapy was mandated by protocol for patients treated with less than mastectomy.

Adj., adjuvant; CT, chemotherapy; BIG, Breast International Group; IQR, interquartile range; RT, radiation therapy; LTM, less than mastectomy.

N− intermediate risk versus 83% of N+ intermediate risk). The individual characteristics that comprise the St Gallen criteria are consistent with the overall risk categorization (Tables 3 and 4); patients with more aggressive disease characteristics (presence of PVI, higher grade tumors, >2 cm tumors, HER2-positive tumors) more often received chemotherapy, a pattern particularly apparent among patients with N− disease.

All patients in TEXT had hormone receptor-positive tumors, of whom only 11% had tumors negative for either ER or PgR (1.5% ER negative and 9.5% PgR negative). Given the caveat of small numbers, higher proportions of N− patients with either ER-negative or PgR-negative tumors received chemotherapy, an observation not apparent in N+ disease (Table 4). For ∼85% of patients, the continuous percentage of ER and PgR immunostaining cells was reported; higher proportions of patients in the N− cohort with tumors expressing very low levels (≤20% expression) of either ER or PgR received chemotherapy (Figure 2).

all factors

CART analysis explored which factors classified patients into subgroups with low or high chemotherapy prescription. The predominant factor was nodal status (Figure 3). Geographical regions formed the next split for patients with both N− and N+ disease. Among patients with N+ disease, two geographical groupings emerged in which 72% versus 94% of patients received chemotherapy, with patient age or presence of PVI as further determinants among the two groupings, respectively. Among patients with N− disease, 32% versus 60% of patients received chemotherapy in two geographical groupings. Among countries choosing chemotherapy less frequently, tumor size and patient age were determinants: patients with ≤1 cm tumors

Table 2. Chemotherapy use by tumor characteristics

	All patients		Total
	No adj. CT	Adj. CT	
Number of patients	321 (36)	569 (64)	890
Node–positive axillary LN			
0	273 (54)	230 (46)	503
1–3	43 (16)	234 (84)	277
4–9	2 (3)	68 (97)	70
10+	0 (0)	32 (100)	32
Unknown	3	5	8
St Gallen risk categories[a]			
Low	67 (81)	16 (19)	83
Intermediate	244 (37)	407 (63)	651
Intermediate N−	203 (49)	211 (51)	414
Intermediate N+	41 (17)	196 (83)	237
High	5 (4)	137 (96)	142

Number (%). Percentages sum across the row.
[a]Fourteen patients could not be completely classified because of missing pathology data.
Adj., adjuvant; CT, chemotherapy; LN, lymph nodes.

Table 3. 2005 St Gallen risk categories [15] (Definition of risk categories for patients with operated breast cancer)

Risk catetory	
Low risk[a]	*Node negative* AND all of the following features: pT ≤2 cm, AND Grade 1[b], AND Absence of peritumoral vascular invasion[c], AND HER2/*neu* gene neither overexpressed nor amplified[d], AND Age ≥35 years
Intermediate risk[e]	*Node negative* AND *at least one* of the following features: pT >2 cm, OR Grade 2–3,[b] OR Presence of peritumoral vascular invasion[c], OR HER2/*neu* gene overexpressed or amplified[d], OR Age <35 years *Node Positive (1–3 involved nodes)* AND HER2/*neu* gene neither overexpressed nor amplified[d]
High risk	*Node positive (1–3 involved nodes)* AND HER2/*neu* gene overexpressed or amplified[d] *Node positive (4 or more involved nodes)*

[a]Some Panel members view pTla and pTlb (i.e. pT<1 cm) tumors with node-negative disease as representing low risk even if higher grade and/or younger age.
[b]Histologic and/or nuclear grade.
[c]Peritumoral vascular invasion was considered controversial as a discriminatory feature of increased risk; its presence defined intermediate risk for node-negative disease, but did not influence risk category for node-positive disease.
[d]HER2/*neu* gene overexpression or amplification must be determined by quality-controlled assays using immunohistochemistry or fluorescence *in situ* hybridization analysis.
[e]Note that the intermediate-risk category includes both node-negative and node-positive 1–3 disease.
pT, pathological tumor size (i.e, size of the invasive component).

least frequently received chemotherapy (13%), whereas patients aged ≤43 years having >1 cm tumors most frequently received chemotherapy (71%). In the countries where chemotherapy was chosen for 60% of patients with N− disease, tumor grade, size and patient age were determinants. The factors that did not appear to play a major role in decision making were ER status, PgR status or HER2 status of the tumor, neither did the continuous percentage of ER and PgR immunostaining cells appear to play a role in the reanalysis among the subset of patients for whom these percentages were available.

discussion

Clearly there is a group of patients with low to intermediate risk of relapse after surgery for early breast cancer for whom chemotherapy adds little or no benefit to combined endocrine therapy, but the oncology community has not been able to recruit to randomized trials designed to investigate this question despite multiple attempts. The premature closure of PERCHE, and of IBCSG Trial 11-93 10 years earlier, because of inadequate accrual demonstrates that when treating premenopausal endocrine-responsive early breast cancer, physicians and/or patients are not willing to allow random chance to decide whether or not to give chemotherapy. Indeed, the 2007 St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer [15] described the selection of whether to give chemotherapy for patients with endocrine-responsive disease 'perhaps the most difficult decision in current adjuvant therapy', mainly because there are only underpowered clinical trial results to aid in this decision. The current absence of sufficient information also challenges decisions to prematurely close trials due to low accrual, with the reason for doing so being that the scientific question will not be relevant long term. However, 10 years after the closure of IBCSG Trial 11-93 the question addressed remains unanswered, and there is no trial planned for the foreseeable future.

We investigated characteristics of patients enrolled in TEXT, where the decision of whether or not to use chemotherapy was determined not by the trial, but at the center, and observed that positive lymph node status was the predominant determinant of chemotherapy choice. Strong geographical patterns were observed also, indicating regional biases, but in spite of preconceived ideas, the United States did not use more chemotherapy in N− populations compared with several other countries. The fact that nodal status was most often used to make the decision reflects a perceived increase in risk of recurrence on the basis of years of research and clinical trials that divided breast cancer patients on the basis of staging. Geographical differences may arise from a variety of sources, including institutional guidelines, national health advisories, insurance coverage, experience with agents such as GnRH

Table 4. Chemotherapy use by tumor characteristics, overall and according to patients' lymph node status

	Lymph node negative		Lymph node positive		All patients		Total
	No Adj. CT	Adj. CT	No Adj. CT	Adj. CT	No Adj. CT	Adj. CT	*N*
All patients	273 (54)	230 (46)	48 (12)	339 (88)	321 (36)	569 (64)	890
Tumor size (cm)							
≤1	83 (78)	24 (22)	8 (24)	25 (76)	91 (65)	49 (35)	140
1.1–2	152 (56)	119 (44)	20 (14)	121 (86)	172 (42)	240 (58)	412
>2	37 (31)	84 (69)	19 (10)	180 (90)	56 (18)	264 (83)	320
Unknown	1	3	1	13	2	16	18
Tumor grade							
1/well	82 (69)	37 (31)	17 (23)	58 (77)	99 (51)	95 (49)	194
2/moderate	159 (56)	127 (44)	23 (13)	161 (88)	182 (39)	288 (61)	470
3/poorly	27 (30)	63 (70)	7 (6)	110 (94)	34 (16)	173 (84)	207
Unknown	5	3	1	10	6	13	19
Peritumoral vascular invasion							
No	229 (58)	168 (42)	31 (20)	124 (80)	260 (47)	292 (53)	552
Yes	37 (42)	52 (58)	13 (6)	197 (94)	50 (17)	249 (83)	299
Unknown/not assessed	7 (41)	10 (59)	4 (18)	18 (82)	11 (28)	28 (72)	39
HER2 status[a]							
Negative	246 (58)	179 (42)	44 (13)	282 (87)	290 (39)	461 (61)	751
Positive	22 (31)	48 (69)	3 (6)	48 (94)	25 (21)	96 (79)	121
Unknown	5	3	1	9	6	12	18
ER/PgR status							
ER−/PgR+	0 (0)	8 (100)	1 (13)	7 (88)	1 (6)	15 (94)	16
ER+/PgR−	14 (35)	26 (65)	6 (13)	39 (87)	20 (24)	65 (76)	85
ER+/PgR+	259 (57)	196 (43)	41 (12)	290 (88)	300 (38)	486 (62)	786
Unknown/missing	0	0	0	3	0	3	3
ER%, median (IQR)[b]	85 (70–90)	80 (67–95)	80 (70–90)	80 (70–90)	85 (70–90)	80 (70–90)	80 (70–90)
PgR%, median (IQR)[b]	80 (50–90)	75 (30–90)	80 (40–90)	70 (25–90)	80 (50–90)	70 (30–90)	75 (37–90)

Number (%) unless otherwise specified. Percentages sum across the row.

[a]HER2 positive if amplified by FISH, or immunohistochemistry (IHC) 3+ and FISH not done.

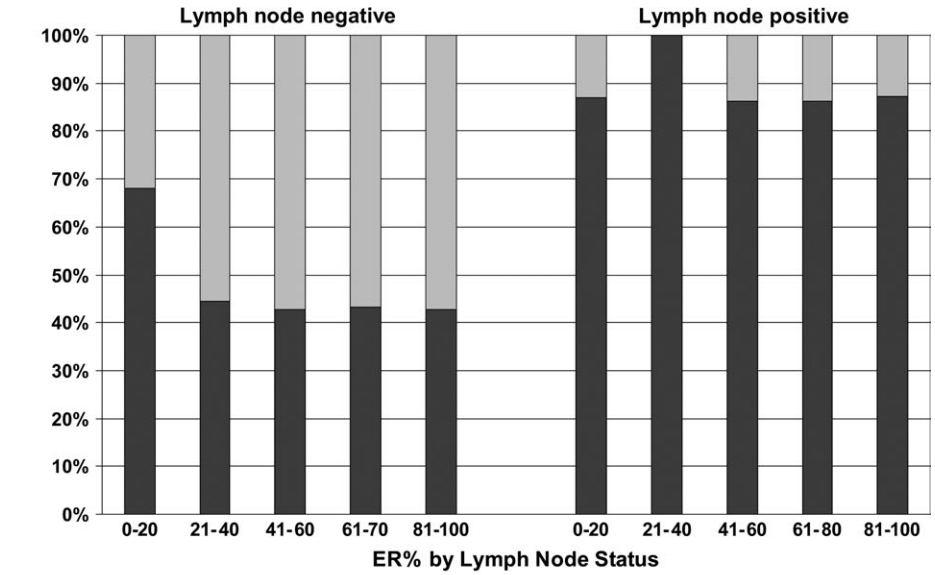
[b]Patients were required to have ER-positive and/or PgR-positive tumors, with positive defined as ≥10% immunostaining cells by IHC; quantitative levels were available for 719 (ER) and 715 (PgR) patients.

Adj., adjuvant; CT, chemotherapy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; PgR, progesterone receptor.

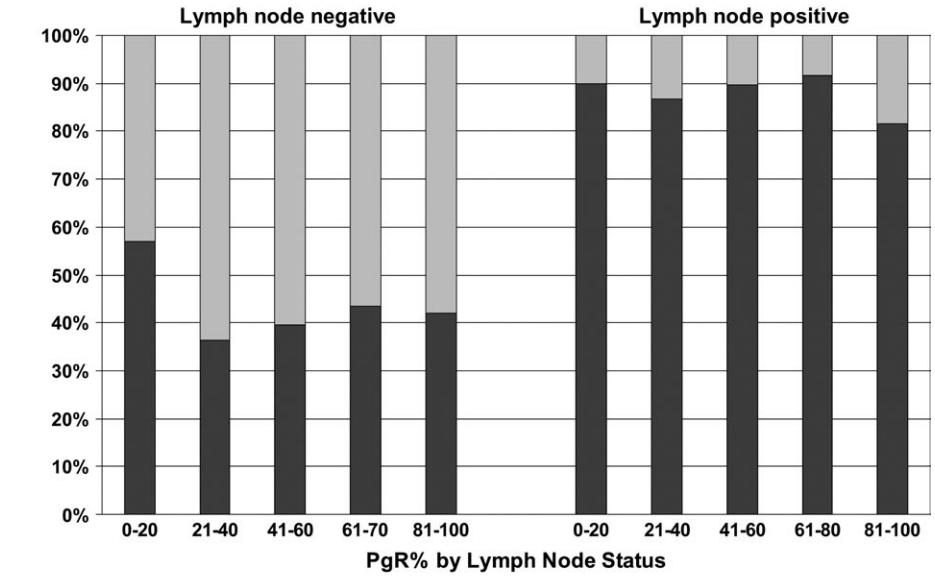
analogues, local opinion leaders' positions and other factors. Randomized clinical trials that remove biases in the perceived value of chemotherapy in the absence of direct evidence of its benefit, however, have been unsuccessful.

Overall, overview analyses and analyses of individual trials have demonstrated a significant benefit for adjuvant chemotherapy compared with no chemotherapy, especially for premenopausal women [1–4]. These analyses have several limitations such as using age <50 years as a proxy for premenopausal status, including a combination of patients with endocrine-responsive and -nonresponsive tumors and sometimes with no hormone receptor assessment, and using possibly less than optimal endocrine treatments. The National Surgical Adjuvant Breast and Bowel Project B-20 trial demonstrated benefit of combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil in addition to tamoxifen versus tamoxifen alone for premenopausal women with endocrine-responsive N− disease [16]. In the recent meta-analysis of adjuvant luteinizing hormone-releasing hormone agonists [5], the addition of OFS plus tamoxifen for patients who receive chemotherapy was beneficial in endocrine-responsive disease with a 26.7% relative reduction in risk of recurrence (95% CI, 38.7% to 12.3% risk reduction; $P = 0.001$). This meta-analysis, however, did not address the question of adding chemotherapy for patients receiving optimal endocrine treatment (the PERCHE question). IBCSG Trial 11-93 [9, 10], which investigated the addition of chemotherapy to combined OFS plus tamoxifen in a small group of patients ($n = 174$), has shown neither benefit from adding chemotherapy nor an indication of a detrimental effect on disease control by avoiding chemotherapy. IBCSG Trial 11-93 continues to be the only published study on the role of adding chemotherapy among premenopausal patients with N+ endocrine-responsive disease who receive combined endocrine therapy with OFS plus tamoxifen. This question will become even more important if the results of the ongoing SOFT demonstrate benefit for the addition of OFS to tamoxifen as adjuvant therapy in premenopausal women.

The 2005 St Gallen Consensus endorsed endocrine responsiveness as the primary disease characteristic to consider



No CT	8	10	24	71	122		3	0	6	14	21
Yes CT	17	8	18	54	91		20	12	38	88	143



No CT	31	21	32	56	95		8	4	5	6	21
Yes CT	41	12	21	43	69		71	26	43	66	93

Figure 2. Chemotherapy use according to estrogen receptor (ER) expression level (top panel) and progesterone receptor (PgR) expression level (bottom panel) of the tumor by immunohistochemistry, according to patients' lymph node status. Expression (*x*-axis) is divided into 20% bins; the table provides the numbers of patients in each bin.

for selection of adjuvant systemic therapy [11], and the 2007 Consensus reaffirmed and refined this position [15]. The endocrine effects of chemotherapy in young women are also well documented [17], indicating the need to tailor therapies according to their relative endocrine and cytotoxic effects. The 2007 St Gallen Consensus [15] panelists accepted either tamoxifen plus OFS or tamoxifen alone as standard endocrine therapies for premenopausal patients. In premenopausal women with endocrine-responsive disease and a low or intermediate risk of recurrence on average, it is possible that a benefit equivalent to that obtained by chemotherapy plus tamoxifen may be achieved by a combination of OFS plus tamoxifen (or possibly an aromatase inhibitor).

Additional biologic factors such as HER2 expression/amplification and/or measures of proliferation might identify patients with endocrine-responsive disease who possibly derive less benefit from endocrine therapy [18]. Several recent studies have indicated that gene expression profiling can distinguish patient subsets deriving different benefit from endocrine treatment and chemotherapy [19–22]. In our analysis,

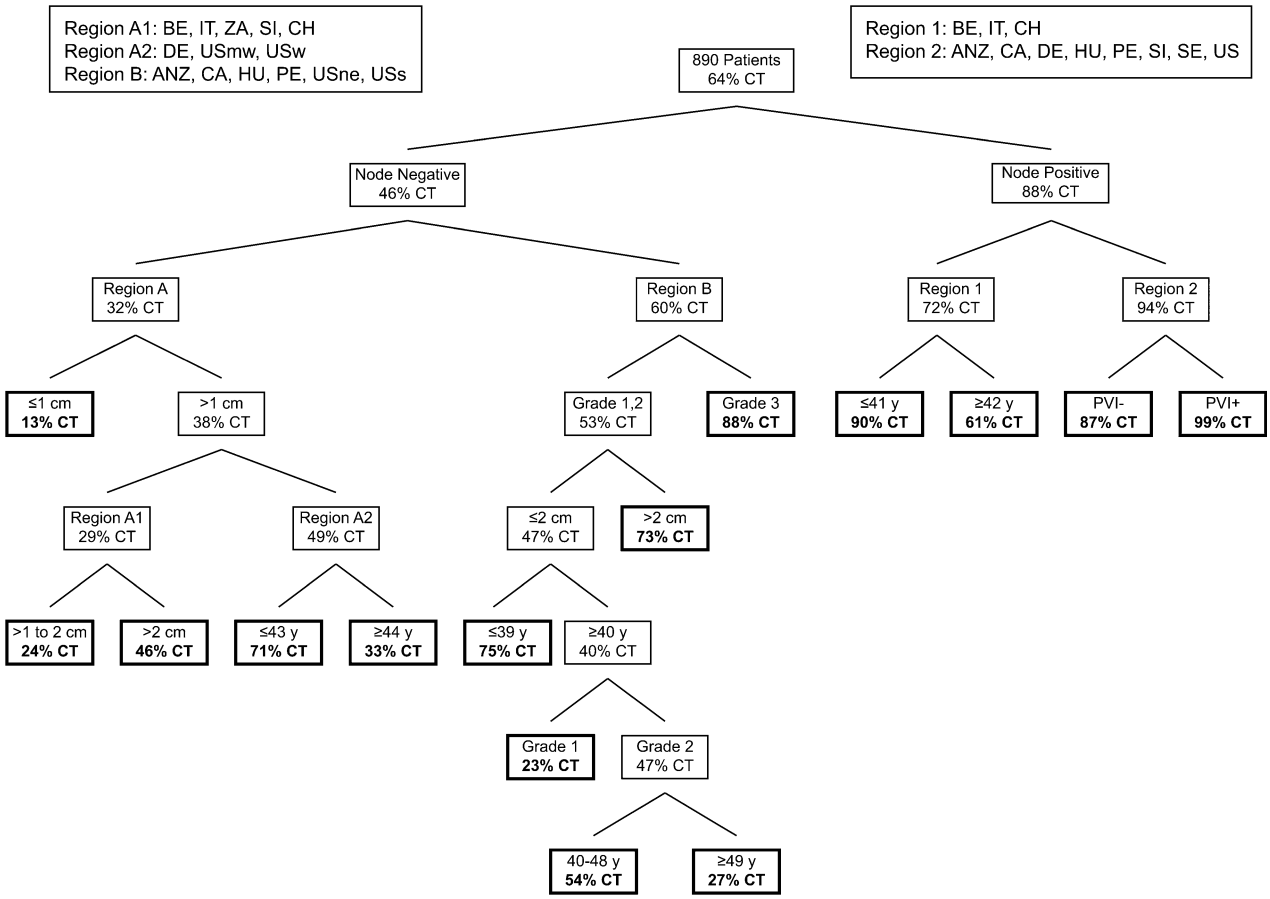


Figure 3. Classification and regression tree analysis exploring which factors classified patients into subgroups with low or high chemotherapy prescription; percentage of patients receiving chemotherapy is provided at each node, with terminal nodes highlighted in bold.

biological characteristics which may help determine the degree of endocrine responsiveness of the tumor such as ER and PgR expression levels and HER2 status did not appear to be major determinants of chemotherapy choice.

The Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) and Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx) trials were launched in 2006 for women with early-stage breast cancer with the objective of validating the utility of signatures of molecular or gene expression profiles in clinical practice [23, 24]. The trials focus on the question of whether these signatures identify a subset of patients with operable N− breast cancer who may not need chemotherapy. Neither trial will be able to address the question posed in the PERCHE trial, for reasons including the lack of statistical power to examine the premenopausal subgroup and the lack of standardized endocrine therapy, the choice of which may be influenced by whether or not the patient is amenorrheic after chemotherapy.

The role of adjuvant chemotherapy, in addition to optimal endocrine therapy, for premenopausal breast cancer patients with endocrine-responsive disease, and in particular those with limited or no nodal involvement, remains unclear. The inability to directly address the question was once again evidenced by the closure of the PERCHE trial after enrolling only 29 patients over a period of more than 3 years. We conclude that the perceived estimation of increased risk of relapse is the primary determinant for using chemotherapy despite uncertainties regarding whether it offers benefit (or degree of benefit) when added to combined endocrine therapy for patients with endocrine-responsive disease.

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Appendix

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