Individualized Prediction of Menses Recovery After Chemotherapy for Early-stage Breast Cancer: A Nomogram Developed From UNICANCER PACS04 and PACS05 Trials

Barbara Pistilli,[1] Chafika Mazouni,[2] Anna Zingarello,[1,3] Matthieu Faron,[2,4] Mahasti Saghatchian,[1] Michael Grynberg,[5] Marc Spielmann,[1] Paul Kerbrat,[6] Henri Roché,[7] Veronique Lorgis,[8] Thomas Bachelot,[9] Mario Campone,[10] Christelle Levy,[11] Anthony Gonçalves,[12] Anne Lesur,[13] Corinne Veyret,[14] Laurence Vanlemmens,[15] Jerome Lemonnier,[16] Suzette Delaloge[1]

Abstract

An accurate and individualized prediction of menses recovery is feasible for premenopausal patients eligible for adjuvant chemotherapy for early-stage breast cancer to better inform the chemotherapy discussion and individualize fertility counseling.

Background: The likelihood of menses recovery varies greatly in premenopausal patients receiving adjuvant chemotherapy for breast cancer. Quantifying this probability for each patient could better inform the chemotherapy discussion and individualize fertility counseling. We performed a pooled analysis of the PACS04 and PACS05 adjuvant randomized trials to develop a nomogram to estimate the probability of menses recovery at 3, 6, and 18 months after the end of adjuvant chemotherapy. **Patients and Methods:** Women who were premenopausal and aged $\leq$ 50 years at randomization in the PACS04 and PACS05 trials were included in the present analysis. The primary endpoint was the probability of menses recovery within 18 months of chemotherapy completion. Multivariable Cox proportional hazards regression was used to estimate the association of each variable with the likelihood of menses resumption. A nomogram was developed to predict menses recovery at different intervals. **Results:** The factors associated with menses recovery were assessed for 1210 patients. At a median follow-up of 90 months (range, 3-189 months), 342 of 1210 patients (28.2%) had recovered menses. The probability of menses recovery at 18 months was 25.5% (range, 23.0%-27.9%). After backward elimination, age, final body mass index, type of chemotherapy, and hormone therapy were selected to build the nomogram to predict the probability of menstrual resumption at 3, 6, and 18 months after chemotherapy. **Conclusion:** An accurate and individualized prediction of menses recovery is feasible for premenopausal patients eligible for adjuvant chemotherapy for early-stage breast cancer. Our nomogram will be externally validated in a large prospective cohort.

Clinical Breast Cancer, Vol. 19, No. 1, 63-70

Keywords: Adjuvant chemotherapy, Chemotherapy induced amenorrhea, Early breast cancer, Menses recovery, Nomogram

[1]Department of Medical Oncology
[2]Department of Surgical Oncology, Institut Gustave Roussy, Villejuif, France
[3]U.O. Oncologia Medica 2, IRCCS AOU San Martino-IST, Genova, Italy
[4]Department of Biostatistics and Epidemiology, Institut Gustave Roussy, Villejuif, France
[5]Department of Reproductive Medicine and Fertility Preservation, Hopital Antoine Béclère, Clamart, and Université Paris Sud XI, Paris, France
[6]Department of Oncology, Centre Eugene Marquis, Rennes, France
[7]Department of Medical Oncology, Institut Claudius Regaud, IUCT Oncopole, Toulouse, France
[8]Department of Medical Oncology, Centre Georges François Leclerc, Dijon, France
[9]Department of Medical Oncology, Centre Léon Bérard, Lyon, France
[10]Department of Medical Oncology, Institut de Cancérologie de l'Ouest, Angers, France
[11]Department of Medical Oncology, Centre Franois Baclesse, Caen, France
[12]Department of Medical Oncology, Institut Paoli-Calmettes, Marseille, France
[13]Department of Medical Oncology, Institut de Cancérologie de Lorriane, Nancy, France
[14]Department of Medical Oncology, Centre Henri Becquerel, Rouen, France
[15]Department of Medical Oncology, Centre Oscar Lambret, Lille, France
[16]National Federation of French Cancer Centres, Paris, France

Submitted: Apr 25, 2018; Revised: Jun 6, 2018; Accepted: Aug 16, 2018; Epub: Aug 23, 2018

Address for correspondence: Barbara Pistilli, MD, Department of Medical Oncology, Institut Gustave Roussy, Villejuif 94800, France
E-mail contact: barbara.pistilli@gustaveroussy.fr

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2018.08.005

Introduction

Currently, ~22% of breast cancer cases are diagnosed in women aged < 50 years in Western countries. In recent years, the prognosis of young patients with breast cancer has improved, mainly by implementation of adjuvant treatments, such as chemotherapy and endocrine therapy.[1] However, because the number of cured patients has been increasing, the long-term side effects of adjuvant treatments have become a major concern in this unique population. Chemotherapy can induce premature ovarian failure in young patients, leading to several consequences affecting patients' long-term quality of life, including hot flashes, sexual impairment, infertility, osteoporosis, sleep disturbances, mood swings, and cognitive dysfunction. In reported series, the rate of amenorrhea related to chemotherapy has ranged from 10% to 93% of premenopausal patients and represents a main concern and source of major psychological distress for a large proportion of young women with early-stage breast cancer.[2,3]

Several mechanisms have been proposed to explain the gonadal toxicity and follicular loss secondary to chemotherapy, albeit some have not been completely elucidated.[4] Also, several cytotoxic anticancer agents can induce apoptosis of growing follicles, ovarian fibrosis with the disappearance of functional follicles, and vascular damage. In addition, a phenomenon termed "burn out of follicle reserve" has been recently described as potentially involved. The phenomenon consists of imbalanced follicle recruitment and growth induced by gonadotoxic agents, which ultimately leads to accelerated depletion of the follicular stockpile.[5]

After adjuvant or neoadjuvant chemotherapy, the likelihood of menses recovery has varied greatly in premenopausal patients with early-stage breast cancer, with a range of 9% to 10% in patients aged ≥ 40 years and 42% to 45.3% in younger patients.[2] This wide range depends on several variables, including the follow-up duration, patient age at the start of treatment, type and schedule of the chemotherapy regimen, and subsequent endocrine therapy. Also, many variables that could influence the resumption of menses are still unknown and others have not been extensively studied, such as smoking, body mass index (BMI), glycemia, dose-dense chemotherapy, and trastuzumab administration. Moreover, the relative "weight" of each variable in affecting ovarian function is unknown; thus, a correct definition of the likelihood of menses recovery for each patient cannot be easily provided. Quantifying this risk could have a prominent role for tailoring the discussion of chemotherapy side effects with young patients, helping chemotherapy decision-making in the case of limited risk/benefit, and individualizing oncofertility counseling by the estimated risk of ovarian failure.[6]

In the present study, we have reported the results of a pooled analysis of 2 randomized trials that tested different adjuvant chemotherapy regimens for patients with localized breast cancer, PACS04 and PACS05. We aimed to develop a user-friendly nomogram to estimate the specific probability of menses recovery for each patient receiving adjuvant chemotherapy for early-stage breast cancer.

Patients and Methods

Patients

Data were selected from 4524 eligible patients with early-stage breast cancer who had participated in the PACS04 and PACS05 randomized adjuvant trials from 2001 to 2007. We identified 1683 women who had been premenopausal and aged ≤ 50 years at diagnosis. Chemotherapy-induced amenorrhea was observed in 1407 patients (83.6%). The factors associated with menses recovery were assessed in 1210 patients. We excluded from the analysis those patients who had recovered menses during chemotherapy and those for whom the date of recovery had not been reported (Figure 1).

Systemic and locoregional therapies were given according to the study design, as previously reported.[7,8] In the PACS04 trial, patients with lymph node-positive breast cancer were randomly assigned to either 6 courses of $FE_{100}C$ (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) or ED_{75} (epirubicin 75 mg/m^2, docetaxel 75 mg/m^2) every 3 weeks with or without 1 year of trastuzumab for patients with human epidermal growth factor receptor 2-positive ($HER2^+$) disease.[7] In the PACS05 trial, patients with lymph node-negative high-risk breast cancer were randomized to 4 or 6 cycles of $FE_{100}C$.[8] In both trials, endocrine therapy was mandatory for patients with estrogen receptor-positive (ER^+) breast cancer. The endocrine therapy was tamoxifen for 5 years for premenopausal patients.

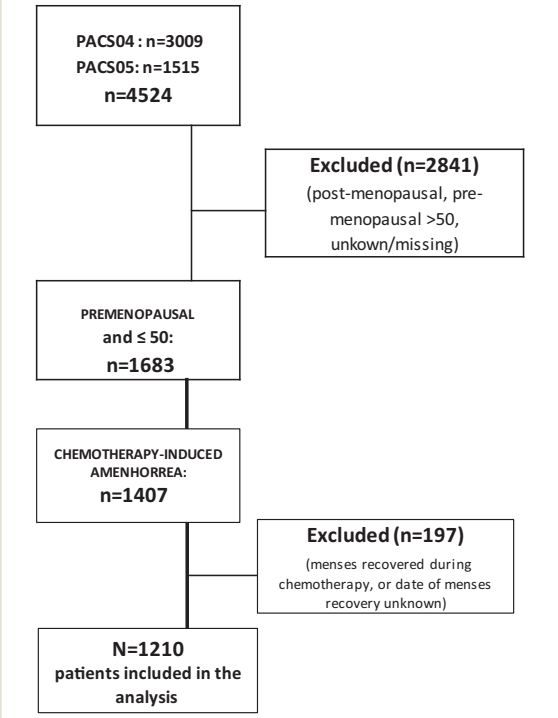
Menopausal status was collected at the beginning of adjuvant chemotherapy. Patients were considered premenopausal if they had had their last menstrual period within the previous 12 months. The menstrual history was reported at baseline, at every cycle, at the end of chemotherapy, and thereafter every 6 months to ≤ 5 years. Clinical, hematologic, and biochemical assessments were performed every 6 months through year 5 and every 12 months thereafter. The regulatory and ethics authorities of all participating centers had approved both trials (ClinicalTrials.gov identifier, NCT00054587 and NCT00055679 for PACS04 and PACS05, respectively).

Statistical Analysis

The primary endpoint was to assess the probability of menses recovery within 18 months of chemotherapy completion. The secondary endpoint was to develop a nomogram to estimate the probability of menses recovery at 3, 6, and 18 months after adjuvant chemotherapy completion using multivariate analysis.

The baseline patient-, tumor-, and treatment-specific characteristics included in the analysis were age at diagnosis (continuous variable), weight and BMI assessed at baseline and at the end of chemotherapy (final BMI), baseline and final glycemia, histologic grade (I, II, III), tumor size (T1, T2, T3, T4), nodal stage (N0, N1, N2/N3), ER and progesterone receptor status (positive vs. negative), HER2 status (positive vs. negative vs. missing), chemotherapy regimen (6 $FE_{100}C$ vs. 4 $FE_{100}C$ vs. 6 ED_{75}), chemotherapy duration, cumulative dose of cyclophosphamide (3000 vs. 2000 vs. 0 mg/m^2), trastuzumab (yes vs. no), and hormonal therapy (yes vs. no). ER and progesterone receptor status were considered positive if ≥ 10% of tumor cells stained positively on immunohistochemical staining. Amenorrhea was defined as interruption of menstruation cycles during chemotherapy, without any menstrual bleeding up to the end of chemotherapy. The prognostic factors of menses recovery after chemotherapy were identified through univariate analysis. Multivariable Cox proportional hazards regression was used to estimate the hazard ratios and 95% confidence intervals for the association between each variable and the

Figure 1 Flowchart of the Study



likelihood of menses recovery. In the multivariate Cox model, a stepwise variable selection procedure was used to select the variables that showed significant associations with menses recovery on univariate analysis. During the selection process, $P < .20$ was required for initial inclusion in the model and $P < .10$ to remain in the model.

Nomogram

Using the data set, a nomogram based on the Cox model was developed to predict for the recovery of menses. The nomogram is a graphic prediction tool for calculating the event probabilities for each individual patient by assigning a number of risk points to each corresponding covariate. The sum of the risk points produces a total risk point score, from which the probability of menses recovery at a specific interval can be assessed.

The endpoint of interest for constructing the nomograms was the probability of menses recovery at 3, 6, and 18 months. A multivariate analysis was conducted using Cox proportional hazards regression. The linearity between the log-hazard and the predictors was tested by introducing orthogonal polynomials in the model. In the case of nonlinearity, the relation was coded with orthogonal polynomials of degree 2 or 3, as appropriate. Forest plots were used to summarize the results. The predictive variables were used to construct the nomogram. Backward elimination was performed to choose the covariates to be retained in the model. The discriminative power of the model was quantified in terms of discrimination and calibration. Internal calibration was explored graphically by plotting the difference between the observed and predicted probabilities. For internal validation, 200 bootstrap resamples were performed. The concordance index was used to measure the nomogram's predictive accuracy.[9,10] All analyses were performed using R statistical software, version 3.4.0 (R Foundation, Vienna, Austria; available at: www.r-project.org).

We also generated a web-based prediction tool from the nomogram to estimate the likelihood of menses recovery at specific points after the end of chemotherapy. This tool will be freely available after external validation of the CANTO (cancer toxicities) cohort.

Results

Study Population

The patient and tumor characteristics of 1210 patients are listed in Table 1. Most patients presented with stage T1, grade I or II, ER^+ tumors. HER2 status was assessed in 1076 patients. HER2 positivity (3+ using immunohistochemistry or fluorescence in situ hybridization amplification) was found in 203 patients (16.8%). Docetaxel (ED_{75}) was administered to 401 patients (33.1%), and 576 patients (47.6%) received 6 $FE_{100}C$ and 233 (19.3%) received 4 $FE_{100}C$. Trastuzumab was given to 122 patients (7.2%) and sequential hormonal therapy to 1229 patients (73%).

Predicting Menses Recovery Using Cox Model

At a median follow-up point of 90 months (range, 3-189 months), 343 of the 1210 patients (28.2%) had recovered their menses cycles at different points. Of the 343 women, 39 had recovered menses at 3 months, 133 at 6 months, and 294 at 12 months (Figure 2). The probability of menses recovery at 18 months was 25.5% (range, 23.0%-27.9%). Menses resumption stratified by age group is listed in Table 2.

Using Cox regression analysis, we found that younger age ($P < .0001$), greater BMI after chemotherapy completion ($P = .07$), chemotherapy without alkylating agents ($P = .004$), and absence of endocrine therapy ($P < .001$) were independently associated with menses recovery (Figure 3).

Using backward analysis, age, BMI after chemotherapy, chemotherapy regimen, and hormonal therapy were selected to build the nomogram to predict the probability of menses recovery at 3, 6, and 18 months after receiving chemotherapy (Figure 4). Although the BMI was of borderline significance, it was included in the risk predictor model and in the risk score estimation to increase the predictive power of the nomogram. For example, a woman aged 36 years (89 points), with a BMI of 30 kg/m^2 at the end of chemotherapy (10 points), who was receiving an alkylating-based regimen (0 point) and hormonal therapy (0 point) would have a total risk point score of 99. This corresponded to a probability of menses recovery of 23% at 3 months, 40% at 6 months, and 48% at 18 months.

The overall predictive accuracy of the model as measured using the concordance index was 0.75. The calibration of the model was assessed graphically. Calibration plots showed good agreement when the nomogram predictions were compared with the actual probability of menses recovery in the 1210 women at 18 months (Figure 5). Finally, we generated a web-based prediction tool using the nomogram for probability calculation of menses recovery at 18 months after the end of chemotherapy to easily estimate the specific risk of gonadotoxicity for each patient during adjuvant treatment

Table 1 Characteristics of Study Population (n = 1210)

Characteristic	n (%)
Age, y	
Median	44
Range	22-50
Age group	
< 34 y	70 (5.8)
35-39 y	213 (17.7)
40-44 y	405 (33.7)
45-50 y	522 (43.5)
Initial BMI, kg/m^2	
Median	22.7
Range	15-57
Final BMI, kg/m^2	
Median	22.9
Range	16-59
Tumor size at surgery, mm	
Median	20
Range	5-180
Tumor size group	
≤ 20 mm	681 (56.3)
> 20 mm	521 (43)
Unavailable	8 (0.7)
Nodal status	
N0	461 (38.1)
N+	749 (61.9)
Histologic grade	
I	88 (7.3)
II	577 (47.7)
III	529 (43.7)
Unknown	16 (1.3)
ER status	
Negative	267 (22)
Positive	943 (78)
PR status	
Negative	298 (24.6)
Positive	838 (69.3)
Unavailable	74 (6.1)
HER2 status	
Negative	873 (72.2)
Positive	203 (16.8)
Unavailable	134 (11)
Adjuvant treatment	
6 ED_{75}	401 (33.1)
6 $FE_{100}C$	576 (47.6)
4 $FE_{100}C$	233 (19.3)
Trastuzumab	81 (6.7)
Hormonal therapy	924 (76.4)

Abbreviations: BMI = body mass index; ED_{75} = epirubicin 75 mg/m^2, docetaxel 75 mg/m^2; ER = estrogen receptor; $FE_{100}C$ = 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2; PR = progesterone receptor.

planning. This program, called MAAT-IGR, will be freely available online through the Gustave Roussy Cancer Campus website.

External validation of the nomogram will be performed in a large multicenter prospective cohort study of patients with early-stage breast cancer, CANTO (ClinicalTrials.gov identifier, NCT01993498; UNICANCER; details available at: http://etudecanto.org/).

Discussion

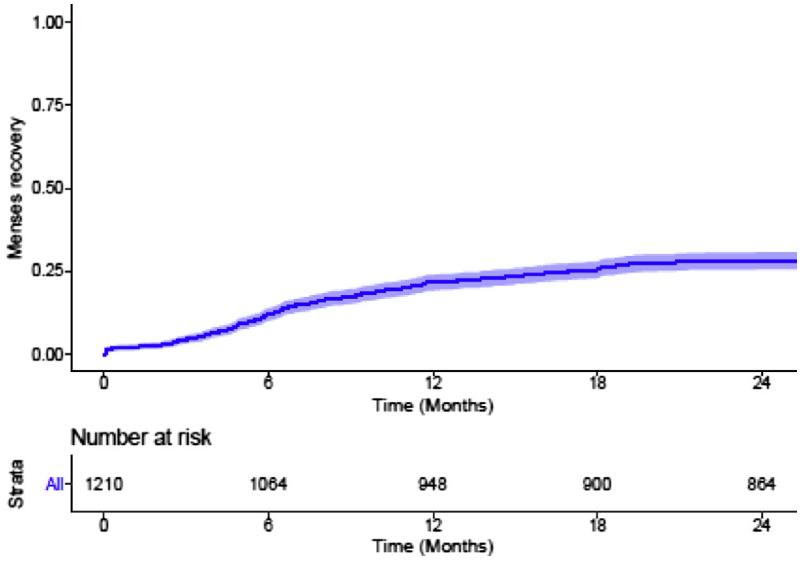
The present analysis aimed to evaluate the patterns and predictors of menses recovery in patients included in the 2 large phase III randomized clinical trials of adjuvant chemotherapy for early-stage breast cancer to provide an easily accessible nomogram for the prediction of menses recovery in premenopausal patients. The main objective of our study was to define the probability of menses recovery within 18 months of chemotherapy completion. In our cohort, very few patients had recovered menses > 18 months after the end of chemotherapy. Because most patients experienced menses resumption within the first 18 months, we analyzed the pattern of menses recovery within this defined interval. In most trials, menses recovery was assessed within 12 months after the end of chemotherapy. However, recent expert consensus guidelines have stated that a longer interval might better detect the likelihood of menses recovery.[11]

We found that 83% of patients developed chemotherapy-induced amenorrhea, confirming that a large proportion of premenopausal women with breast cancer will be affected. At median follow-up of 90 months, only 28% of the patients had recovered their menstrual cycles; therefore, most patients maintained a condition of amenorrhea. The high rate of persistent amenorrhea reported in our analysis was likely dependent on the age cutoff of 50 years we had used for patient selection. Thus, ~40% of women were in their perimenopausal time.

Consistent with much reported data, we found a greater incidence of amenorrhea in women aged 40 to 49 years, and patient age was the strongest predictor of menses recovery after chemotherapy, independently of other variables.[12-16] Menses resumed in 63% of patients aged < 35 years, 55% of those aged 35 to 39 years, and only 19.7% of patients aged 40 to 50 years.

In our model, considering age as a continuous variable, we observed a nonlinear relationship between age and the probability of recovering menses. Overall, this probability tended to decrease as patient age increased, with a greater decrease in older patients. Moreover, younger women were more likely to recover menses earlier after the end of chemotherapy, with the duration of amenorrhea consistently shorter in the youngest patients. Generally, very young patients aged < 35 years tended to remain premenopausal, and > 80% experienced menstrual cycle recovery by 6 months after the end of chemotherapy.[17,18] In contrast, for patients aged 35 to 40 years, the likelihood of permanent menopause after chemotherapy was greater, with the risk increasing with increasing age.[19] In addition, the number and quality of oocytes decrease over time with increasing age. For every 1-year increase in age, a 20% increase in the odds of developing chemotherapy-related amenorrhea has been estimated.[20]

Figure 2 Menses Recovery Over Time ≤ 24 Months After the End of Adjuvant Chemotherapy



In our model, we found that a higher BMI at the end of chemotherapy was associated with a greater likelihood of menstrual resumption, although we could not define a specific BMI threshold. Other studies investigating the risk factors for chemotherapy-induced amenorrhea did not find a statistical significant association between BMI and ovarian failure.[21,22] The correlation between BMI and menses recovery is likely to be related to the increased level of estrogens throughout the menstrual cycles normally found in healthy premenopausal women with a greater BMI. It has been shown that an increase of 10% in accumulated body fat was associated with a 5- to 7-pmol/L increase in estradiol levels. IN contrast, weight loss, secondary to calorie restriction, results in a reduction in circulating estrogens and inhibition of menstrual cycles.[23-25]

Although the effect of a single agent in inducing amenorrhea is not easily assessable, because multiple drugs are routinely used in adjuvant treatment, it is largely known that alkylating agents induce a greater incidence of amenorrhea. The incidence of amenorrhea associated with cyclophosphamide has ranged from 18% to 97% according to patient age, with a greater likelihood of being irreversible in older women.[16,26] In our analysis, patients who had not received cyclophosphamide-containing chemotherapy had a greater likelihood of recovering menses. However, comparing 2 different cumulative doses of cyclophosphamide (2000 mg/m^2 vs. 3000 mg/ m^2), we did not find a statistically significant correlation with the probability of menses resumption. Consistently, previous data have shown that larger cumulative doses of cyclophosphamide do not significantly induce greater rates of amenorrhea compared with lower doses.[27,28]

Table 2 Menses Resumption Stratified by Age Group

Age, y	Menses Recovery/Amenorrhea (n = 342/1201)
< 35	43/68 (63.2)
35-39	117/210 (55.7)
40-50	182/923 (19.7)

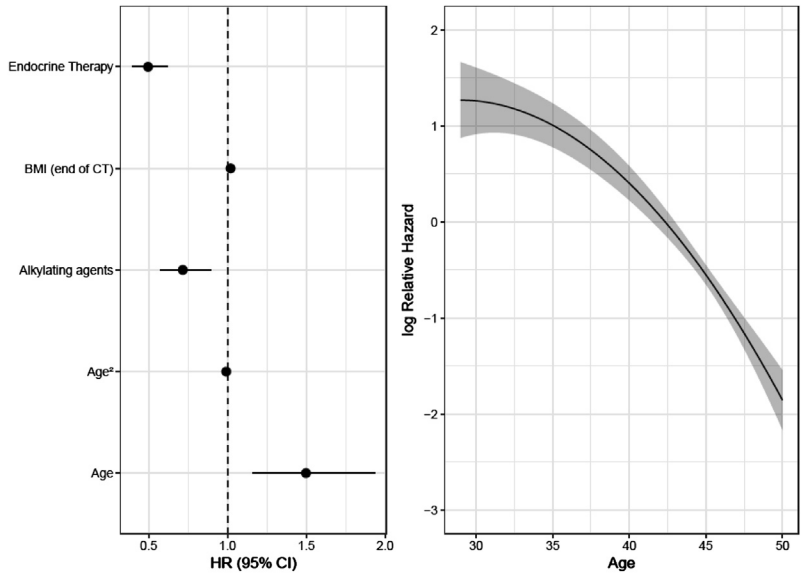
Data presented as n/N (%).

The effect of taxanes on menses has not been clearly defined, because the results have not been consistent throughout the reported data.[29-31] However, a recent meta-analysis of 15 studies showed that taxane exposure for early-stage breast cancer was a negative factor for menses recovery (odds ratio, 0.49; 95% confidence interval, 0.30-0.80; $P = .004$).[32] In our analysis, docetaxel did not affect menses recovery; thus, taxanes were not included in the final nomogram. However, 2 relevant confounding factors should be considered in the present series. First, docetaxel was given only in combination with epirubicin and not as sequential treatment to previous chemotherapy with anthracyclines and cyclophosphamide. Second, the dose per cycle was lower than that currently used in adjuvant chemotherapy for breast cancer at 75 mg/m^2 instead of 100 mg/m^2, albeit the cumulative dose was comparable (450 mg/m^2).

Several studies have argued that different doses, durations, and schedules of anthracyclines might correlate with menses recovery. However, interpretation of the existing data is challenging, with contrasting findings reported across several trials. A retrospective analysis of the French Adjuvant Study Group of 8 adjuvant studies showed a greater rate of amenorrhea in women who had received 4 to 6 cycles of anthracycline-based chemotherapy rather than 1 to 3 cycles.[33] In contrast, we did not find any statistically significant correlation between the number of cycles of anthracycline-based chemotherapy and the likelihood of menses recovery.

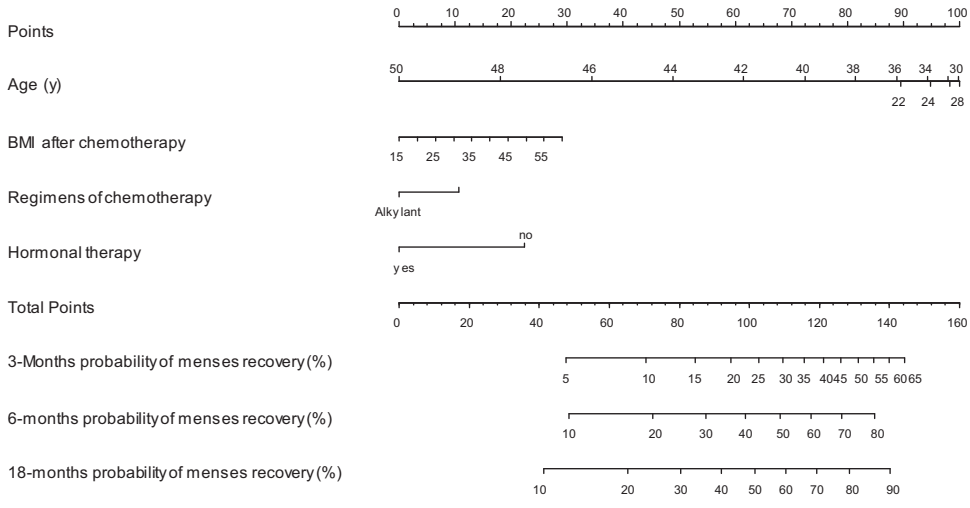
In our series, 75% of the patients had ER$^+$ disease, and 73% had received adjuvant tamoxifen for ~5 years. Similar to previous reports, tamoxifen use after chemotherapy was independently associated with a decreased probability of menses resumption at different intervals ($P < .001$). Several prospective trials have demonstrated that tamoxifen administration significantly affected

Figure 3 (Left) Variables Independently Associated With Menses Recovery. The Quadratic Term in the Age Variable Accounted for Nonlinearity of the Relation Between Age and Probability of Recovering Menses. (Right) Overall, This Probability Tended to Decrease With Age, Showing a Greater Decrease in Older Patients



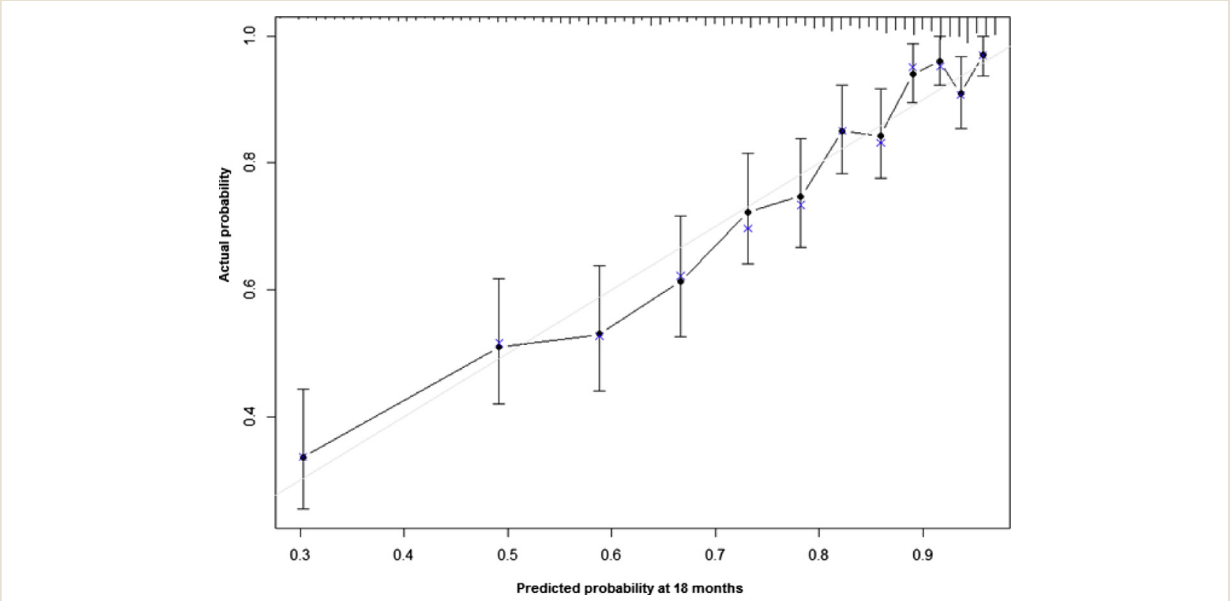
Abbreviations: BMI = body mass index; CI = confidence interval; CT = chemotherapy; HR = hazard ratio.

Figure 4 Nomogram for Prediction of Menses Recovery at 3, 6, and 18 Months After End of Adjuvant Chemotherapy. The Likelihood of Menses Recovery Was Calculated by Summing the Risk Points, Determined From the Patient- and Treatment-specific Characteristics. For Each Variable, the Number of Associated Risk Points Can Be Determined by Drawing a Vertical Line Straight Up From the Variable to the Corresponding Value on the Axis With the Risk Points (range, 0-100). The Assigned Points for All 4 Variables Are Summed. The Total Is Provided on the Total Points Line. Once the Total Has Been Located, a Vertical Line is Drawn Between the Total Points Line and the Lines Reporting the Percentage Estimation of Menses Recovery at Different Intervals



Abbreviation: BMI, body mass index.

Figure 5 Calibration Curve for 18-month Menses Recovery. The Calibration Curve Shows the Predictions From the Nomogram Compared With the Actual Probability for the 1210 Patients



the duration of chemotherapy-induced amenorrhea.[27-33] The role of tamoxifen in chemotherapy-induced amenorrhea seems related to the increased plasma estradiol concentration induced by the drug, unbalancing the hypothalamic-ovarian feedback loop.

The strengths of our analysis included the large sample size, exclusion of patients who had recovered menses during chemotherapy, homogeneity of the collected data because the patients had been randomized in phase III clinical trials, and the availability of systematic long-term follow-up data, which enabled us to assess the likelihood of menses recovery at different intervals. However, some limitations should be discussed. We assumed that the patients who had recovered menses were those for whom $\geq$ 1 episode of menstrual cycle resumption had been reported. However, we could not achieve information regarding the duration and regularity of menses and pregnancies, and we did not have any quantitative assessment of ovarian activity measured by ultrasound evaluation of the antral follicle count or serum levels of follicle-stimulating hormone, estradiol, inhibin-B, and anti-Müllerian hormone. Furthermore, many other variables potentially affecting the ovarian reserve during chemotherapy and the recuperation of menses were not available from our records. These included previous hormonal contraception, age at menarche, number of previous pregnancies, any thyroid or autoimmune dysfunction, and so forth. These factors might play a prominent role in ovarian function of healthy women and, potentially, in the recuperation of menses after adjuvant chemotherapy. Therefore, they should be extensively investigated in both retrospective and prospective cohorts. Moreover, the final BMI but not the BMI at baseline was significantly associated with menses recovery. Thus, this variable makes our model less suitable for risk assessment before starting chemotherapy, because it was built using the clinical data available at the end of treatment. However, because the BMI is a modifiable variable, further investigations of its role in menses recovery are warranted to better inform patients eligible for adjuvant chemotherapy.

Finally, another weakness to be considered is that only internal validation was performed by bootstrapping resamples. Therefore, further external validation on a separate prospective cohort, as already planned, could provide additional information regarding the model.

Conclusion

Our analysis, conducted on a large premenopausal cohort, has confirmed the possibility of developing a user-friendly nomogram for individualizing the prediction of menses recovery at different intervals after adjuvant chemotherapy. The individual likelihood of ovarian function recovery should be addressed when discussing the long-term side effects of chemotherapy with premenopausal patients, not only to better select patients who should receive oncofertility counseling, but also to adequately inform patients of their risk of developing early menopause and the related physical and psychological symptoms. Furthermore, physician awareness of the probability of menses recovery might better guide decisions about endocrine therapy, because women in their 40s with prolonged amenorrhea after chemotherapy can resume menses when receiving treatment with aromatase inhibitors.[12,13] After external validation, this model could become a graphic and easily available tool for assessing the likelihood of menses resumption for each premenopausal patient eligible for chemotherapy for early-stage breast cancer.

Clinical Practice Points

- After adjuvant or neoadjuvant chemotherapy, the likelihood of menses recovery is highly variable in premenopausal patients

with early-stage breast cancer, and many clinical factors influencing the resumption of menses are still unknown or have not been extensively studied.

- We found that at median follow-up of 90 months, only 28% of patients had recovered their menstrual cycles; therefore, most patients maintained a condition of amenorrhea.
- Age, final BMI, type of chemotherapy, and hormonal therapy were significantly associated with menstrual resumption.
- Our analysis has confirmed the possibility of developing a user-friendly nomogram for individualizing the prediction of menses recovery at different points after adjuvant chemotherapy to better refer patients for oncofertility counseling and also to adequately inform young women of their risk of developing early menopause.

Acknowledgments

We thank all investigators and their supporting staff. We also thank all the members of R&D UNICANCER, especially Mrs Lise Roca, for data collection and assembly.

Disclosure

The authors declare that they have no competing interests.

References

1. De Santis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin* 2014; 64:52-62.
2. Torino F, Barnabei A, De Vecchis L, et al. Chemotherapy-induced ovarian toxicity in patients affected by endocrine-responsive early breast cancer. *Crit Rev Oncol Hematol* 2014; 89:27-42.
3. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst* 2012; 104:386-405.
4. Partridge AH, Ruddy KJ, Gelber S, et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. *Fertil Steril* 2010; 94:638-44.
5. Blumenfeld Z. Chemotherapy and fertility. *Best Pract Res Clin Obstet Gynaecol* 2012; 26:379-90.
6. Lambertini M, Del Mastro L, Pescio MC, et al. Cancer and fertility preservation: international recommendations from an expert meeting. *BMC Med* 2016; 14:1.
7. Spielmann M, Roché H, Delozier T, et al. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. *J Clin Oncol* 2009; 27:6129-34.
8. Kerbrat P, Coudert B, Asselain B, et al. Optimal duration of adjuvant chemotherapy for high risk node negative breast cancer patients: 6-year results of the prospective randomized phase III UNICANCER-PACS-05 trial (UCBG-0106). *Eur J Cancer* 2017; 79:166-75.
9. Steyerberg EW, Harrell FE, Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001; 54:774-81.
10. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 15:361-87.
11. Paluch-Shimon S, Pagani O, Partridge AH, et al. Second International Consensus Guidelines for breast cancer in young women (BCY2). *Breast* 2016; 26:87-99.
12. Bonadonna G, Valagussa P, Moliterni A, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med* 1995; 332:901-6.
13. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006; 24:5769-79.
14. Dohou J, Mouret-Reynier MA, Kwiatkowski F, et al. A retrospective study on the onset of menopause after chemotherapy: analysis of data extracted from the Jean Perrin Comprehensive Cancer Center Database concerning 345 young breast cancer patients diagnosed between 1994 and 2012. *Oncology* 2017; 92:255-63.
15. Meng K, Tian W, Zhou M, et al. Impact of chemotherapy-induced amenorrhea in breast cancer patients: the evaluation of ovarian function by menstrual history and hormonal levels. *World J Surg Oncol* 2013; 11:101.
16. Kil WJ, Ahn SD, Shin SS, et al. Treatment-induced menstrual changes in very young (<35 years old) breast cancer patients. *Breast Cancer Res Treat* 2006; 96:245-50.
17. Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J Clin Oncol* 2006; 24:1045e51.
18. Hortobagyi GN, Buzdar AU, Marcus CE, et al. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at MD Anderson Hospital and Tumor Institute. *Natl Cancer Inst Monogr* 1986; 1:105e9.
19. Bianco AR, Del Mastro L, Gallo C, et al. Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer. *Br J Cancer* 1991; 63:799-803.
20. Ruddy KJ, O'Neill A, Miller KD, et al. Biomarker prediction of chemotherapy-related amenorrhea in premenopausal women with breast cancer participating in E5103. *Breast Cancer Res Treat* 2014; 144:591-7.
21. Zavos A, Valachis A. Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis. *Acta Oncol* 2016; 55:664-70.
22. Abusief ME, Missmer SA, Ginsburg ES, et al. Relationship between reproductive history, anthropometrics, lifestyle factors, and the likelihood of persistent chemotherapy-related amenorrhea in women with premenopausal breast cancer. *Fertil Steril* 2012; 97:154-9.
23. Kirchengast S, Huber J. Body composition characteristics and fat distribution patterns in young infertile women. *Fertil Steril* 2004; 81:539-44.
24. van Binsbergen CJ, Coelingh Bennink HJ, Odink J, et al. A comparative and longitudinal study on endocrine changes related to ovarian function in patients with anorexia nervosa. *J Clin Endocrinol Metab* 1990; 71:705-11.
25. Warren MP. Effects of undernutrition on reproductive function in the human. *Endocr Rev* 1983; 4:363-77.
26. Castiglione-Gertsch M, O'Neill A, Price KN, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003; 95:1833-46.
27. Pagani O, O'Neill A, Castiglione M, et al. Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: results of the International Breast Cancer Study Group (IBCSG) trial VI. *Eur J Cancer* 1998; 34:632-40.
28. Parulekar WR, Day AG, Ottaway JA, et al, National Cancer Institute of Canada Clinical Trials Group. Incidence and prognostic impact of amenorrhea during adjuvant therapy in high-risk premenopausal breast cancer: analysis of a National Cancer Institute of Canada Clinical Trials Group Study—NCIC CTG MA.5. *J Clin Oncol* 2005; 23:6002-8.
29. Swain SM, Land SR, Ritter MW, et al. Amenorrhea in premenopausal women on the doxorubicin-and-cyclophosphamide-followed-by-docetaxel arm of NSABP B-30 trial. *Breast Cancer Res Treat* 2009; 113:315-20.
30. Partridge AH. Ovarian suppression for prevention of premature menopause and infertility: empty promise or effective therapy? *J Clin Oncol* 2012; 30:479-81.
31. Boccardo F, Rubagotti A, Bruzzi P, et al. Chemotherapy versus tamoxifen versus chemotherapy plus tamoxifen in node-positive, estrogen receptor-positive breast cancer patients: results of a multicentric Italian study. Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group. *J Clin Oncol* 1990; 8:1310-20.
32. Silva C, Caramelo O, Almeida-Santos T, et al. Factors associated with ovarian function recovery after chemotherapy for breast cancer: a systematic review and meta-analysis. *Human Reprod* 2016; 31:2737-49.
33. Borde F, Chapelle-Marcillac I, Fumoleau P, et al. Role of chemo-induced amenorrhea in premenopausal, node-positive, operable breast cancer patients: 9-year follow-up results of French Adjuvant Study Group data base. *Breast Cancer Res Treat* 2003; 82:S30 (abstract 138).