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ORIGINAL ARTICLE

Primary tumor and patient characteristics in breast cancer as predictors of adjuvant therapy regimen: a regression model

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Abstract
Purpose Adjuvant therapy reduces the risk of recurrence of breast cancer. This study was undertaken to determine characteristics guiding choice of adjuvant therapy.
Methods A retrospective review was completed of characteristics of patients with breast cancer (stages I–III) at a regional center from 2004 to 2007. Univariate analysis was used to select factors ($P < 0.1$) for entry into multivariate stepwise logistic regressions. Odds ratios with 95% confidence intervals were calculated. A P value of <0.05 was significant, and comparisons were two-tailed.
Results Model 1 ($n = 744$) assessed the prescription of any adjuvant regimen (hormonal or chemotherapy). Indicators of choice of any regimen were positive lymph nodes [OR 16.5, CI (6.2, 44.0)], grade [4.0, (2.5, 6.0)], size [3.2, (2.1, 4.6)], PR [0.3, (0.1, 0.6)], and multicentricity [0.2 (0.04, 0.66)]. Model 2 ($n = 663$) assessed chemotherapy in ER+ patients. Indicators of addition of chemotherapy were stage [8.9 (4.3, 18.6), grade [5.5 (3.1, 9.6)], positive nodes [2.7 (1.1, 6.4)], physician experience [1.1 (1.0, 1.2)], age [0.8 (0.79, 0.86)], and year of treatment [0.8, (0.4, 0.9)]. Model 3 ($n = 867$) assessed prescription of a more aggressive chemotherapy regimen and indicators were treatment by a breast specialist oncologist [8.6 (1.7, 43.1)], stage [3.6 (2.4, 5.4)], positive nodes [2.6 (1.7, 4.1)], year of treatment [1.5 (1.3, 1.8)], size [1.2 (1.1, 1.4)], age [0.91 (0.89, 0.93)], and PR [0.4 (0.3, 0.6)].
Conclusions This study verifies known factors for choice of adjuvant therapy, excludes others thought to be important, and quantifies effects at our center. Further studies are required to compare these models where risk stratification is different.

Keywords Chemotherapy · Hormonal therapy · Breast cancer · Risk stratification · Regression model

Introduction

Breast cancer is the most commonly diagnosed cancer in women in Canada, constituting 27.8% of new diagnoses [1, 2]. The estimate for deaths from breast cancer is second after lung cancer, at about 15% of all female cancer patients [2, 3]. The current standard of care for the treatment of breast cancer is multidisciplinary, including surgery, radiation therapy, chemotherapy, and hormonal therapy.

Patients with early-stage breast cancer (Stages I and II) will experience a 15–20% treatment failure when treated with surgery alone, highlighting the fact that breast cancer can be considered a systemic rather than local disease process [4]. Adjuvant chemotherapy has been found to be effective in reducing the risk of distant relapse of breast cancer and has contributed to the steady decline in breast cancer mortality [5]. The intent is to eliminate any micrometastatic disease before it can progress into clinical disease. However, the choice to treat with chemotherapy must

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be balanced with the potential short- and long-term toxicities of these agents.

Removal and histologic examination of axillary lymph nodes have been deemed an important step in obtaining staging information and in regional control of the disease, though it does not appear to confer a survival benefit [6–8]. Pathological information after surgical resection, including primary tumor characteristics, is prognostically important and helps us to guide further therapies. Axillary nodal status remains the most important feature for defining post-operative risk for distant relapse and subsequent need for adjuvant chemotherapy [9]. In addition to lymph node status, the St. Gallen International Consensus Conference defined the primary breast cancer characteristics necessary to assess for the need for adjuvant systemic therapy, including primary tumor size, estrogen receptor (ER) and progesterone receptor (PR) status, and HER2/neu expression [9]. This consensus statement includes classifications for low, intermediate, and high risk of relapse and suggests the choice of adjuvant regimen be based on these categories, with more aggressive regimens being given to more aggressive cancers. Other organizations have developed similar consensus statements [10]. The 2010 National Comprehensive Cancer Network (NCCN) guidelines classify invasive breast cancers based initially on ER/PR and Her2/neu status. Tumor size and lymph node status as components of stage are then used to determine the need for adjuvant chemotherapy [11]. This classification is similar to that of the 2010 European Society of Medical Oncology (ESMO) guidelines for systemic therapy, again identifying the most relevant factors for systemic therapy decision making as ER and Her2 status [12]. The ESMO guidelines also directly identify multigene assays such as Oncotype DX score as important to systemic therapy decision making, as is patient preference, which is difficult to quantify in retrospective reviews.

The cyclophosphamide, methotrexate, and 5-fluorouracil treatment regimen (CMF) was initially considered standard chemotherapy [13]. The anthracyclines, doxorubicin, and epirubicin have subsequently become the mainstay of adjuvant chemotherapy, in combination with cyclophosphamide (AC, CEF, FEC). The taxanes, paclitaxel, and docetaxel, when combined with anthracyclines, have been found, in node positive patients, to provide a longer disease-free survival than anthracyclines alone [14, 15]. Combination anthracycline and taxane regimens include FEC-D (5-fluorouracil, epirubicin, cyclophosphamide, and docetaxel), AC/T (adriamycin, cyclophosphamide, and taxol), and dose-dense AC/T.

There is a vast literature regarding risk stratification of patients with breast cancer after initial surgical therapy. Loprinzi showed through questionnaires that oncologists used prognostic variables, in particular patient age, tumor size, positive nodes, and ER/PR status for patients differently, and that estimates for these patients regarding 10-year disease-free survival varied greatly [16].

From such uncertainty, the program Adjuvant!Online was created [17]. This web-based program provides a tool for oncologists to use patient and tumor factors such as age, comorbidites (minor, major), ER status, grade, size, and number of positive nodes to generate an estimate of 10-year disease-free survival and possible benefit derived from chemotherapy or hormonal therapy. Although such tools exist and are used frequently, the ultimate decision regarding chemotherapy or choice of particular regimen is that of the prescribing oncologist and the personal choice of the patient.

The current study aimed to determine and quantify which patient and tumor factors are associated first with the prescription of any adjuvant regimen (hormonal or chemotherapy), the addition of chemotherapy to hormonal therapy in patients with ER+ tumors, and the prescription of a more aggressive chemotherapy regimen over less intensive regimens. In effect, this study is one of the decision-making process that is inherently important to systemic therapy in the treatment of breast cancer.

Methods

This is a retrospective cross-sectional study. Data for consecutive patients diagnosed with invasive breast cancer having received treatment at a Regional Cancer Center from 2004 to 2007 were collected from the institution database. Inclusion criteria were female gender and diagnosis of invasive breast cancer. Exclusion criteria included age greater than 75 years, neoadjuvant chemotherapy, and metastatic disease at diagnosis. Research ethics board approval was obtained prior to initiation of this study.

Eighteen risk factors or independent variables identified in the literature or in practice were collected for each patient, including age, year of treatment, family history of breast cancer in a first-degree relative, medical oncologist name and years of experience, comorbidities including renal/hepatic dysfunction, diabetes mellitus, a cardiac history including myocardial infarction, angina, or congestive heart failure, or a history of neuropathy. Tumor-specific information included histologic type (infiltrating ductal/lobular or other), tumor size (cm), grade (I, II, or III), stage (I, II, or III), margin status (defined as positive surgical margin, even if re-resected), multifocality, multicentricity, ER and PR status, Her2/neu status, axillary lymph node status including number of positive nodes, and total number harvested. The lymph node variable was defined in two ways: node positivity (any number of positive lymph nodes) and pathologic nodal status [N1 (0–3 positive nodes);

Table 1 Current risk stratification and chemotherapy regimens at Juravinski Cancer Center, Hamilton, Ontario, Canada

Risk category	Pre-menopausal	Post-menopausal
Intermediate risk	AC	AC
	CMF	CMF
High risk	CEF	*Healthy*
		FEC/D
	AC/T	AC/T
	ddAC/T	ddAC/T
		Older
		AC
		CMF

AC adriamycin, cyclophosphamide, *CMF* cyclophosphamide, methotrexate, 5-fluorouracil, *CEF* cyclophosphamide, epirubicin, 5-fluorouracil, *AC/T* adriamycin, cyclophosphamide, taxol, *ddAC/T* dose-dense adriamycin, cyclophosphamide, taxol, *FEC/D* 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel

N2 (4–9 positive nodes); N3 (>9 positive nodes)]. The comorbidities considered for analyses were cardiac, renal/hepatic, diabetes mellitus, and neuropathy. They were combined as any comorbidity versus no comorbidity because of the small numbers in each category.

Chemotherapy regimens used within the last 4 years at our center were identified as AC, CMF, CEF, AC/T, ddAC/T (dose dense), and FEC/D (Table 1). AC and CMF, generally used for patients at low or intermediate risk of relapse, were chosen as the standard, and the remaining four regimens were considered aggressive chemotherapy, reserved for higher-risk patients. In the current study, the dependent variable was defined as treatment with any regimen, hormonal or chemotherapy (Model 1), any chemotherapy regimen (Model 2), and more aggressive chemotherapy regimen (Model 3).

For sample size estimation, we used the recommendation of Peduzzi et al. [18] that at least 10 events per covariable are used to avoid poor estimation of Wald-based confidence intervals (CI) and Wald test of coefficients. To have at least 80% power, a minimum of 400 patients would be required considering 20 patients per 18 risk factors, with 2 possible treatment outcomes for all three models. To maintain power, univariable analyses were performed to identify candidate variables to include in the multivariable model. Categorical variables were reported as counts and percentages and compared with chi-squared or Fisher's exact test. Continuous variables were reported as mean and standard deviation (SD) and compared with *t* test for independent samples. All variables with a *P* value of 0.10 or less were included in the multivariable analyses. Binary logistic regression analysis was employed to assess the relationships between the independent variables and any of the three dependent variables of the three models.

Odds ratios (OR), 95% confidence intervals (CI), and Hosmer–Lemeshow goodness-of-fit values are reported for each analysis. A *P* value of <0.05 was considered for statistical significance. Data analysis was performed using SPSS statistical software version 18.0 (SPSS Inc., Chicago IL).

Results

From 2004 to 2007, 2,143 patients were referred to a Regional Cancer Center with the diagnosis of invasive breast cancer. According to exclusion criteria, 1,685 consecutive patients were reviewed and data entered into the regression analysis.

Model 1 ($n = 744$) assessed the choice of any adjuvant regimen over no adjuvant regimen. Table 2 presents the results of univariable analyses. Using multivariable regression analysis (Table 3), factors that were most important for a physician to initiate any adjuvant treatment included positive lymph nodes [OR 16.5, CI (6.2, 44.0)], higher grade [4.0, (2.5, 6.0)], larger tumor size [3.2, (2.1, 4.6)], PR negativity [0.3, (0.1, 0.6)], and absence of multicentric disease [0.2 (0.04, 0.66)]. The *P* value for Hosmer–Lemeshow goodness of fit was 0.402, indicating data fit the model moderately well. Variables not found to have a significant effect on the initiation of treatment were year of treatment, age, histologic type, stage, ER, Her2/neu, margin status, $N_1/N_2/N_3$ status, family history, multifocal disease, and comorbidities.

Model 2 ($n = 663$) assessed the choice of any chemotherapy regimen in addition to hormonal therapy over hormonal therapy alone (tamoxifen or aromatase inhibitor) in patients with ER+ tumors. Table 4 summarizes the results of univariable analyses. Using multivariable analysis, six independent variables correlated with choice of chemotherapy over hormonal therapy only, including higher stage [8.9 (4.3, 18.6), higher grade [5.5 (3.1, 9.6)], positive nodes [2.7 (1.1, 6.4)], attending physician's years of experience [1.1 (1.0, 1.2)], younger age [0.8 (0.79, 0.86)], and more recent year of treatment [0.8. (0.4, 0.9)] (Table 5). Variables not found to have a significant effect on the choice of chemotherapy included family history, comorbidities, histologic type, margin status, multifocality, multicentricity, PR, Her2/neu, $N_1/N_2/N_3$ status, breast specialist medical oncologist, and year of treatment. The Hosmer–Lemeshow goodness-of-fit *P* value for this model was 0.941, indicating there was an excellent fit of the data to the regression model.

Model 3 ($n = 867$) assessed the choice of aggressive chemotherapy regimen (FEC-D, AC/T, ddAC/T, or CEF) over AC/CMF. Table 6 presents the results of univariable analyses. Using multivariable regression analysis, seven independent variables correlated with choice of aggressive

Table 2 Model 1: univariable comparison of no therapy to any therapy

	No therapy *n* (%)	Any therapy *n* (%)	*P* value
Age at treatment mean ± SD	61.5 ± 8.7	55.1 ± 10.4	<0.001
Histology			
Infiltrating ductal/lobular	645 (95.6)	997 (98.8)	<0.001
Other[a]	30 (4.4)	12 (1.2)	
Tumor stage			
I	521 (77.0)	292 (29.4)	<0.001
II	134 (20.0)	525 (52.9)	
III	21 (3.0)	176 (17.7)	
Tumor grade			
I	306 (45.8)	127 (12.8)	<0.001
II	209 (46.3)	463 (46.5)	
III	53 (7.9)	406 (40.8)	
Estrogen receptor positivity	626 (93.7)	713 (71.0)	<0.001
Progesterone receptor positivity	529 (79.4)	582 (57.9)	<0.001
Tumor size (cm) (mean ± SD)	1.4 ± 1.0	2.7 ± 1.7	<0.001
Her2/neu positivity	25 (8.4)	171 (25.8)	<0.001
Multicentric disease	16 (5.6)	23 (2.3)	0.009
Multifocal disease	78 (23.0)	96 (9.5)	<0.001
Positive surgical margins	56 (8.6)	105 (10.4)	0.235
Positive nodes (any)	64 (9.5)	452 (47.1)	<0.001
Pathologic nodal status			
N_1	655 (97.6)	846 (84.7)	<0.001
N_2	13 (1.9)	108 (10.8)	
N_3	3 (0.4)	45 (4.5)	
Any comorbidity	79 (12.1)	95 (9.4)	0.085
Family history	117 (18.0)	126 (12.5)	0.002
Year of treatment			
2004	188 (27.8)	216 (21.4)	<0.001
2005	148 (21.9)	223 (23.1)	
2006	150 (22.2)	313 (31.0)	
2007	190 (28.1)	247 (24.5)	

Hormonal therapy, chemotherapy or both

[a] Tubular, mucinous, medullary, adenoid cystic, papillary

regimen including treatment by a breast specialist medical oncologist [8.6 (1.7, 43.1)], stage [3.6 (2.4, 5.4)], positive nodes [2.6 (1.7, 4.1)], recent year of treatment [1.5 (1.3, 1.8)], larger tumor size [1.2 (1.1, 1.4)], younger age [0.91 (0.89, 0.93)], and negative PR [0.4 (0.3, 0.6)]. Factors insignificant included comorbidities, histology, Her2/neu, $N_1/N_2/N_3$ status, and margin status (Table 7). The Hosmer–Lemeshow goodness-of-fit *P* value for this model was 0.706, indicating data fit the regression model well.

Table 3 Model 1: multivariable analysis of no therapy versus any therapy

Variable	Odds ratio	95% CI	*P* value
Positive nodes	16.5	6.2, 44.0	<0.001
Grade	4.0	2.5, 6.0	<0.001
Tumor size	3.2	2.1, 4.6	<0.001
Progesterone receptor	0.3	0.1, 0.6	0.001
Multicentric disease	0.2	0.04, 0.66	0.012

P value for Hosmer–Lemeshow goodness-of-fit test = 0.402

Discussion

The choice of prescribing chemotherapy or a particular regimen as adjuvant therapy for breast cancer is based on a number of factors including characteristics of the patient and of the tumor and patient preference. In integrating these factors, a system such as Adjuvant! Online (http://www.adjuvantonline.com) can be utilized to assist in determining which patients should receive hormonal therapy, chemotherapy, or a more aggressive chemotherapy regimen. The goal is to assist physicians in estimating the risk of negative outcome, i.e., cancer-related mortality or recurrence. These estimates are created from information entered about individual patients and their tumors. Although particular factors such as lymph node status, ER status, and tumor size are important, it is unclear how in practice this integration of factors occurs and which particular factors play a more significant role in these choices.

This study aimed to determine and quantify which factors are associated with choice of any adjuvant regimen (chemotherapy or hormonal), the choice of addition of chemotherapy to hormonal therapy in ER+, and thus lower-risk patients, and the choice of more aggressive chemotherapy regimen over less intensive regimens at our center. Model 1 indicates the factors important to initiation of any adjuvant therapy were positive lymph nodes, high tumor grade, larger tumor size, PR negativity, and the absence of multicentric disease. The absence of multicentric disease as an indicator for treatment might be due to the small number of patients with such features in this database.

Model 2 identifies factors important to the addition of chemotherapy to hormonal therapy in patients with ER+ tumors. Factors associated with the addition of chemotherapy included advanced stage, higher grade, positive lymph nodes, medical oncologist's years of experience, younger age, and more recent year of treatment.

Model 3 was created to address the question of how more aggressive chemotherapy regimens are chosen over less aggressive AC/CMF chemotherapy. From this model,

Table 4 Model 2: univariable comparison of hormonal therapy alone versus hormonal therapy plus chemotherapy in ER^+ patients

	Hormonal therapy *n* (%)	Hormonal and chemotherapy *n* (%)	*P* value
Age at treatment mean ± SD	64.3 ± 8.4	53.2 ± 9.7	<0.001
Histology			
Infiltrating ductal/lobular	105 (99.1)	601 (99.0)	1.0
Other[a]	1 (0.9)	12 (1.0)	
Tumor stage			
I	63 (63.0)	131 (21.9)	<0.001
II	36 (36.0)	339 (56.6)	
III	1 (1.0)	129 (21.5)	
Tumor grade			
I	39 (37.5)	84 (14.0)	<0.001
II	61 (58.7)	340 (56.9)	
III	4 (3.8)	174 (29.1)	
Progesterone receptor positivity	83 (78.3)	497 (82.0)	0.347
Tumor size (cm) (mean ± SD)	2.0 ± 1.6	2.8 ± 1.7	<0.001
Her2/neu positivity	7 (14.6)	104 (25.6)	0.110
Multicentric disease	1 (0.9)	17 (2.9)	0.498
Multifocal disease	9 (8.5)	61 (10.0)	0.725
Positive surgical margins	5 (4.7)	76 (12.5)	0.019
Positive nodes	17 (17.0)	348 (57.6)	<0.001
Pathologic nodal status			
N_1	99 (99.0)	496 (82.1)	<0.001
N_2	1 (1.0)	80 (13.2)	
N_3	0 (0.0)	29 (4.6)	
Any comorbidity	13 (12.3)	48 (7.9)	0.136
Family history	18 (17.0)	72 (11.9)	0.154
Year			
2004	0 (0.0)	144 (23.7)	<0.001
2005	15 (14.2)	154 (25.4)	
2006	84 (79.2)	153 (25.2)	
2007	7 (6.6)	156 (25.7)	
Breast specialist medical oncologist	105 (99.1)	571 (97.9)	0.703
Attending physician's years of experience	10.2 ± 4.6	12.2 ± 6.1	<0.001

[a] Tubular, mucinous, medullary, adenoid cystic, papillary

Table 5 Model 2: multivariate hormonal therapy alone versus hormonal therapy plus chemotherapy in ER+ patients

Variable	Odds ratio	95% CI	*P* value
Tumor stage	8.9	4.3, 18.6	<0.001
Tumor grade	5.5	3.1, 9.6	<0.001
Positive nodes	2.7	1.1, 6.4	0.026
Attending physician's years of experience	1.1	1.0, 1.2	0.011
Age	0.8	0.79, 0.86	<0.001
Year	0.8	0.4, 0.9	0.010

P value for Hosmer–Lemeshow goodness-of-fit test = 0.941

it was evident that the factors that predicted aggressive chemotherapy included treatment by a breast specialist medical oncologist, advanced stage, positive lymph node status, more recent year of treatment, larger tumor size, younger age, and progesterone receptor negativity. As patients with distant metastases were excluded from this study, the stage variable is a composite of tumor size and lymph node status. However, lymph node positivity, indicating any positive lymph nodes regardless of number, was found to be a predictor of more aggressive chemotherapy regimen, independent of TNM stage.

From all three models, it is apparent that at our center only a small proportion of proposed factors have an effect on the choice of a more aggressive chemotherapy regimen or chemotherapy over hormonal therapy alone during the study period. In comparison with current publications such as the British NHS guidelines for early and locally advanced breast cancer, decisions are recommended to be made clinically based on a small number of tumor factors

Table 6 Model 3: univariable standard chemotherapy versus aggressive chemotherapy regimen

	Chemotherapy regimens[a]		*P* value
	AC/CMF *n* (%)	Other regimens *n* (%)	
Age at treatment mean ± SD	57.4 ± 9.8	52.0 ± 9.6	<0.001
Histology			
Infiltrating ductal/lobular	314 (99.1)	683 (98.6)	0.755
Other[b]	3 (0.9)	9 (1.4)	
Tumor stage			
I	155 (49.4)	71 (12.3)	<0.001
II	137 (43.6)	352 (61.1)	
III	22 (7.0)	153 (26.6)	
Tumor grade			
I	31 (9.9)	56 (14.1)	0.033
II	159 (50.8)	243 (42.2)	
III	123 (39.3)	277 (48.1)	
Estrogen receptor positivity	221 (69.9)	386 (66.4)	0.296
Progesterone receptor positivity	190 (59.9)	308 (53.2)	0.058
Tumor size (cm) (mean ± SD)	2.2 ± 1.2	3.1 ± 1.9	<0.001
Her2/neu positivity	41 (22.5)	123 (28.5)	0.135
Multicentric disease	7 (2.2)	14 (2.4)	1.00
Multifocal disease	28 (8.8)	59 (10.1)	0.557
Positive margins	31 (9.8)	69 (11.8)	0.376
Positive nodes	85 (28.4)	350 (62.8)	<0.001
Pathologic nodal status			
N_1	296 (93.7)	448 (77.2)	<0.001
N_2	15 (4.7)	92 (15.9)	
N_3	5 (1.6)	40 (6.9)	
Any comorbidity	36 (11.4)	46 (7.9)	0.090
Family history	39 (12.3)	69 (11.8)	0.831
Year			
2004	93 (29.3)	123 (21.1)	<0.001
2005	95 (30.0)	123 (21.1)	
2006	69 (21.8)	158 (27.1)	
2007	60 (18.9)	179 (30.7)	
Breast specialist medical oncologist	303 (95.6)	580 (99.5)	<0.001
Attending physician's years of experience	12.3 ± 6.1	12.0 ± 6.0	0.467

[a] FEC/D, CEF, AC/T, ddAC/T

[b] Tubular, mucinous, medullary, adenoid cystic, papillary

such as ER and Her2neu [23]. This again is similar to the ESMO and NCCN guidelines.

Although the variables that have been found to be important are interesting, what are more so are the factors that are not deemed important. A number of patient characteristics such as comorbidities are not taken into consideration. This may be due to exclusion of elderly patients in this study (>75 years). However, it would be expected that such pre-existing medical issues may play a role in the younger patient population, in particular when choosing more toxic regimens with more significant side-effect profiles. Family history also does not appear to be important, which is unexpected as it is known to be a risk factor for development of breast cancer, and not necessarily for risk of recurrence.

Surgically determined factors such as positive surgical margin status and heavy node positivity (N_2/N_3 status) were also not found to be important in any model. Lymph node positivity has often been identified as the most important predictive factor in the choice of chemotherapy, based on published algorithms [9–11]. However, the current study indicates that once a patient has been deemed to be node positive at our center, further quantifying this through pathologic $N_1/N_2/N_3$ status did not influence the prescribed regimen. Thus, in the case of a patient being considered for adjuvant chemotherapy with a positive sentinel lymph node biopsy result, a completion axillary lymph node dissection is not predicted to change the choice of adjuvant therapy or particular regimen.

Table 7 Model 3: multivariate standard chemotherapy versus aggressive chemotherapy regimen

Variable	Odds ratio	95% CI	*P* value
Breast specialist	8.6	1.7, 43.1	0.009
Positive nodes	2.6	1.7, 4.1	<0.001
Tumor stage	3.6	2.4, 5.4	<0.001
Year	1.5	1.3, 1.8	<0.001
Tumor size	1.2	1.1, 1.4	0.006
Age	0.91	0.89, 0.93	<0.001
Progesterone receptor	0.4	0.3, 0.6	<0.001

P value for Hosmer–Lemeshow goodness-of-fit test = 0.706

A recent study of adjuvant chemotherapy prescribed to lymph node-negative, hormone receptor–positive patients at NCCN centers indicated younger patients with fewer comorbidities were more likely to receive chemotherapy [19]. Patients with larger tumors, ER or PR negativity, higher grade, positive lymphovascular invasion, and Her2/neu positivity were also more likely to receive chemotherapy [20]. There was also significant variance as to rates of chemotherapy administration from site to site for this cohort. This study is in keeping with the current study, as younger patients with tumor factors that may predict aggressive behavior such as higher grade and larger tumor size were more likely to receive the addition of chemotherapy to hormonal therapy, or a more aggressive chemotherapy regimen.

The practice pattern at our center seems to be similar among medical oncologists. Similar practice patterns at our center may be due in part to multidisciplinary breast cancer case conferences, a breast disease site group providing leadership and guidance, and organization of our clinics into multidisciplinary clinics including medical oncology, radiation oncology, and surgical oncology, facilitating a culture of case discussion. In addition, most medical oncologists at our center deal with only one or two disease sites, contributing to further homogeneity of practice through subspecialization.

Although this study involved analyzing the prescription of particular adjuvant therapy regimens, it is clear that a "standard chemotherapy regimen" does not exist. Trudeau comments on this topic and the current chemotherapy regimens in use, and that the decision-making process for choice of particular regimen may involve issues such as physician preference and training, cost, and patient preference [21]. Province-wide formulary guidelines are currently being developed, which may also affect regimens chosen for patients. Furthermore, growing institutional support for multidisciplinary case conferences, both in academic and in non-academic centers, may impact decision making in the future. These facts highlight the importance of interpreting the present data from a regional and specific center perspective only, given the variability of the aforementioned factors in the prescription and receipt of systemic therapy. However, the availability of information from the current study can permit a more focused assessment of systemic therapy use at our center for the improvement and design of future studies.

This study has certain limitations inherent to the nature of observational studies. The patients were retrieved from the institutional database that was not developed for research purposes. The retrospective design is prone to missing data points, which affected sample size. For example, Her2/neu was not tested routinely for all patients in 2004. However, the study was powered for Model 1 as the primary objective of this study. We decided to present the results based on the available data. Data were missing >10% for variables like Her2/neu and multicentricity, and the application of any method (such as multiple imputation) for handling missing data is misleading. This is a single-center study that may limit its application to other cancer centers with different patient populations and patient volumes.

This study was unable to capture the role of patient preference in decision making for adjuvant therapy. Patient preference and decision making have been studied previously at our center with a Decision Board design [22]. This study showed that providing information to patients both through the initial consultation with a medical oncologist and through Decision Board intervention provided patients with greater satisfaction in the decision-making process, although the number of patients that ultimately chose chemotherapy in the intervention group did not differ from the group that received a medical oncologist consultation alone. Future studies regarding selection of adjuvant therapies warrant the addition of a patient preference variable, although this may be difficult to achieve.

Despite the limitations of current study, important factors have been identified that play important roles in medical oncologist behavior toward prescribing chemotherapy and particular regimens. This study is important as it is one of the first introspective studies to identify and quantify the effects of patient and tumor factors that affect decision making in systemic therapy, specifically at our center. Further multicenter prospective studies, where risk stratification is different, are warranted to provide the decision-making guidelines to medical oncologists in the systemic therapy of breast cancer.

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Conflict of interest None.

References

1. Canadian Cancer Society/National Cancer Institute of Canada (2009) Canadian cancer statistics 2009. Toronto
2. Canadian Cancer Society's Steering Committee (2009) 2009 Canadian cancer statistics. Canadian Cancer Society, Toronto
3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
4. Newman LA, Singletary SE (2007) Overview of adjuvant systemic therapy in early stage breast cancer. Surg Clin N Am 87:499–509
5. Peto R, Boreham J, Clark M et al (2000) UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69. Lancet 355(9217):1822
6. Fisher B, Montague E, Redmond C (1980) Findings from NSABP Protocol No. B-04. Comparison of radical mastectomy with alterative treatments for primary breast cancer. Cancer 46:1–13
7. Moore M, Kinne D (1997) Axillary lymphadenectomy: a diagnostic and therapeutic procedure. J Surg Oncol 66:2–6
8. Jeruss JS, Sener SF, Brinkmann EM, Bilimoria MM, Barrera E, Alwawi E, Nickolov A, Schermerhorn GM, Winchester DJ (2005) Axillary recurrence after sentinel node biopsy. Ann Surg Oncol 12(1):34–40
9. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ, Members Panel (2005) Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 16:1569–1583
10. Shelley W, Trudeau M, the Breast Cancer Disease Site Group (2002) Systemic therapy for node negative breast cancer. Practice guideline report #1-8. Cancer Care Ontario. http://www.cancercare.on.ca
11. NCCN practice guidelines in oncology: breast cancer, v.1, 2010. http://www.nccn.org
12. Aebi S, Davidson T, Gruber G, Castiglione M. On Behalf of the ESMO Guidelines Working Group. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl5):v9–v14
13. Anonymous (1998) Polychemotherapy for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 352(9132):930–942
14. Feig BW, Berger DH, Fuhrman GM (eds) (2006) The M.D. Anderson surgical oncology handbook, 4th edn. Lippincott Williams & Wilkins
15. Early Breast Cancer Trialists Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet 365:1687–1717
16. Loprinzi CL, Ravdin PM, De Laurentiis M, Novotny P (1994) Do American oncologists know how to use prognostic variables for patients with newly diagnosed primary breast cancer? J Clin Oncol 12(7):1422–1426
17. Adjuvant! Online—http://www.adjuvantonline.com
18. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49(12):1373–1379
19. Hassett MJ, Hughes ME, Niland JC, Edge SB, Theriault RL, Wong Y-N, Wilson J, Carter WB, Blayney DW, Weeks JC (2008) Chemotherapy use for hormone receptor-positive, lymph node-negative breast cancer. J Clin Oncol 26(34):5553–5560
20. Fisher B, Dignam J, Wolmark N, DeCillis A, Emir B, Wickerham DL, Bryant J, Dimitrov NV, Abramson N, Atkins JN, Shibata H, Deschenes L, Margolese RG (1997) Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 89(22):1673–1682
21. Trudeau M, Charbonneau F, Gelmon K, Laing K, Latreille J, Mackey J, McLeod D, Pritchard K, Provencher L, Verma S (2005) Selection of adjuvant chemotherapy for the treatment of node positive breast cancer. Lancet Oncol 6:886–898
22. Whelan T, Sawka C, Levine M, Gafni A, Reyno L, Willan A, Julian J, Dent S, Abu-Zahra H, Chouinard E, Tozer R, Pritchard K, Bodendorfer I (2003) Helping patients make informed choices: a randomized trial of a decision aid for adjuvant chemotherapy in lymph node-negative breast cancer. J Natl Cancer Inst 95:581–587
23. National Institute for Health and Clinical Excellence (NHS) Guidelines 2009. Early and locally advanced breast cancer: diagnosis and treatment