Original Article

Risk Factors for Locoregional Disease Recurrence After Breast-Conserving Therapy in Patients With Breast Cancer Treated With Neoadjuvant Chemotherapy: An International Collaboration and Individual Patient Meta-Analysis

Antonios Valachis, MD, PhD[1]; Eleftherios P. Mamounas, MD[2]; Elizabeth A. Mittendorf, MD, PhD[3]; Naoki Hayashi, MD, PhD[4]; Makoto Ishitobi, MD, PhD[5,6]; Clara Natoli, MD[7]; Florian Fitzal, MD[8]; Isabel T. Rubio, MD, PhD[9]; Daniel G. Tiezzi, MD, PhD[10]; Hee-Chul Shin, MD[11]; Stewart J. Anderson, PhD[12]; Kelly K. Hunt, MD[3]; Naoko Matsuda, MD[4]; Shozo Ohsumi, MD[13]; Athina Totomi, MSc[1]; and Cecilia Nilsson, MD, PhD[14]

BACKGROUND: Several studies have reported a high risk of local disease recurrence (LR) and locoregional disease recurrence (LRR) in patients with breast cancer after neoadjuvant chemotherapy (NCT) and breast-conserving therapy (BCT). The objective of the current study was to identify potential risk factors for LR and LRR after NCT and BCT. **METHODS:** Individual patient data sets from 9 studies were pooled. The outcomes of interest were the occurrence of LR and/or LRR. A 1-stage meta-analytic approach was used. Cox proportional hazards regression models were applied to identify factors that were predictive of LR and LRR, respectively. **RESULTS:** A total of 9 studies (4125 patients) provided their data sets. The 10-year LR rate was 6.5%, whereas the 10-year LRR rate was 10.3%. Four factors were found to be associated with a higher risk of LR: 1) estrogen receptor-negative disease; 2) cN + disease; 3) a lack of pathologic complete response in axilla (pN0); and 4) pN2 to pN3 disease. The predictive score for LR determined 3 risk groups: a low-risk, intermediate-risk, and high-risk group with 10-year LR rates of 4.0%, 7.9%, and 20.4%, respectively. Two additional factors were found to be associated with an increased risk of LRR: cT3 to cT4 disease and a lack of pathologic complete response in the breast. The predictive score for LRR determined 3 risk groups; a low-risk, intermediate-risk, and high-risk group with 10-year LRR rates of 3.2%, 10.1%, and 24.1%, respectively. **CONCLUSIONS:** BCT after NCT appears to be an oncologically safe procedure for a large percentage of patients with breast cancer. Two easy-to-use clinical scores were developed that can help clinicians to identify patients at higher risk of LR and LRR after NCT and BCT and individualize the postoperative treatment plan and follow-up. ***Cancer* 2018;124:2923-30.** © *2018 American Cancer Society.*

KEYWORDS: breast cancer, breast-conserving therapy, individual patient meta-analysis, locoregional disease recurrence, neoadjuvant.

INTRODUCTION

Neoadjuvant chemotherapy (NCT) traditionally has been used in the setting of locally advanced and inflammatory breast cancer to convert inoperable tumors to surgically resectable disease.[1,2] Within the last decade, neoadjuvant therapy has been used increasingly in patients with earlier stage disease. Although to our knowledge there are no differences with regard to overall survival outcomes for patients receiving NCT versus adjuvant chemotherapy,[3] NCT facilitates increased rates of breast-conserving therapy (BCT),[4] reduces the incidence of positive lymph nodes, and allows for the in vivo assessment of tumor response to chemotherapy.[5,6] The response to NCT also provides prognostic information.[7,8]

Although several studies to date have reported a high risk of local disease recurrence (LR) or locoregional disease recurrence (LRR) after NCT and BCT,[9-11] others have reported LRR rates of <10%.[12,13] This discrepancy suggests a need to identify risk factors that can predict which patients are at higher risk of LR or LRR after this treatment approach. The identification of risk factors may allow for improved decision making with respect to locoregional therapies.

Corresponding author: Antonios Valachis, MD, PhD, Centre for Clinical Research Sormland, 63188 Mälarsjukhuset, Uppsala University, Sweden; antonis.valachis@igp.uu.se; valachis@hotmail.com

[1]Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden; [2]Comprehensive Breast Program, University of Florida Health Cancer Center-Orlando Health, Orlando, Florida; [3]Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [4]Department of Breast Surgery, St. Luke's International Hospital, Tokyo, Japan; [5]Department of Breast Surgery, Osaka International Cancer Institute, Osaka, Japan; [6]Department of Endocrine Surgery, Osaka International Cancer Institute, Osaka, Japan; [7]Department of Oral, Medical and Biotechnological Sciences, University G. D'Annunzio, Chieti-Pescara, Italy; [8]Department of Surgery, Breast Health Center, Medical University Vienna, Vienna, Austria; [9]Breast Surgical Oncology, Breast Cancer Center, University Hospital VAll d'Hebron, Barcelona, Spain; [10]Breast Disease Division, Department of Gynecology and Obstetrics, Ribeirao Preto Medical School, University of Sao Paulo, Sao Paulo, Brazil; [11]Department of Surgery, Chung-Ang University Hospital, Seoul, South Korea; [12]National Surgical Adjuvant Breast and Bowel Project Biostatistical Center, Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; [13]Department of Breast Oncology, NHO Shikoku Cancer Center, Matsuyama, Japan; [14]Centre for Clinical Research, Vastmanlands County Hospital, Vasteras, Sweden

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Several risk factors for LR or LRR after NCT and BCT have been identified, and 4 predictive risk scores have been proposed.[14-17] However, the clinical usefulness and generalizability of the proposed risk scores are limited by the relatively small sample size in the studies used to develop the scores,[14,15,17] the use of single-institution data,[14,15,17] and the lack of validation in independent data sets.[15-17] However, the development of a predictive score in this treatment setting that could overcome these limitations would be important to help clinicians and patients with decision making regarding BCT after NCT.

The current study was undertaken to identify potential risk factors for LR and LRR after NCT and BCT through a pooled analysis of individual patient data from available cohorts, and to provide a clinical score that may predict the risk of LR and LRR after NCT and BCT.

MATERIALS AND METHODS

Search Strategy

A comprehensive systematic electronic search was conducted through PubMed, without year or language restriction, by using the following keywords: neoadjuvant OR induction OR preoperative OR primary AND breast cancer AND breast-conserving therapy OR BCT OR BCS OR breast-conserving surgery. The search was updated in January 2016.

We also conducted secondary referencing by manually reviewing the reference lists of potentially eligible articles. In addition, the bibliographies of selected review articles were reviewed to ensure that other relevant publications were included.

Trial Eligibility and Selection Criteria

Two researchers independently assessed the articles for inclusion at both the title and abstract phase and the full-text review phase of searching for eligible trials. Disagreements were resolved by discussion.

Studies were considered eligible if they fulfilled all the following criteria: 1) studies that investigated the risk factors for LR or LRR in patients with BCT after NCT, irrespective of the type of chemotherapy used; and 2) studies that reported at least 1 risk factor for LR or LRR. We excluded case reports; studies that investigated risk factors for LRR after NCT and mastectomy; studies that investigated risk factors for distant disease recurrence, overall disease recurrence, or overall survival after NCT and BCT but did not report separate data regarding LRR; and studies that have been presented at scientific meetings only and have not been published in full text.

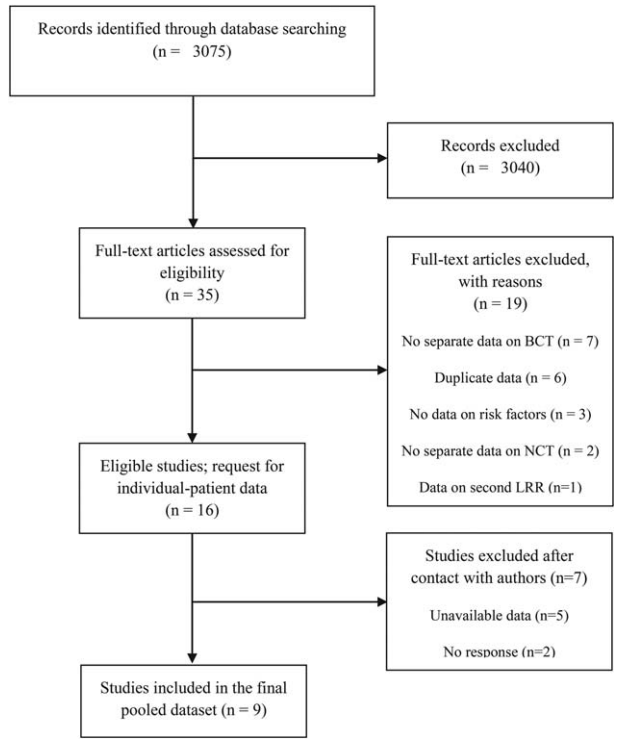

Figure 1. Flowchart diagram for study selection. BCT indicates breast-conserving therapy; NCT, neoadjuvant chemotherapy; LRR, locoregional disease recurrence.

An invitation was sent to all the primary investigators of the eligible studies to determine their interest in an international collaborative study of risk factors for LRR after NCT and BCT. Institutional research ethics board approval was obtained.

Construction of the Consortium

Of 3075 potentially relevant publications, 35 were retrieved for full-text evaluation. Sixteen studies met the inclusion criteria. Of the 16 eligible cohorts, 9 research groups provided individual patient data (Fig. 1).[15-23]

Individual patients were included in the analysis if they had received NCT and underwent BCT to include breast-conserving surgery (BCS) and radiotherapy. Patients who did not receive radiotherapy after surgery were excluded.

Data Collection

The following data were requested from each group for each individual patient: age, menopausal status, tumor size at the time of diagnosis, T classification at the time of diagnosis, N classification at the time of diagnosis, tumor histology (ductal, lobular, medullary, or other), estrogen receptor (ER) status, progesterone receptor (PR) status,

tumor grade, human epidermal growth factor receptor 2 (HER2) status, the presence of lymphovascular invasion, Ki-67, pathologic complete response (pCR), definition of pCR used, size of residual tumor, morphology of residual tumor (solitary mass, multifocal residual disease), surgical margin status (positive, close < 2 mm, or negative) number of positive lymph nodes, type of neoadjuvant chemotherapy (NCT), neoadjuvant trastuzumab therapy, postoperative radiotherapy (breast, regional lymph node irradiation), dose of radiotherapy, use of boost, postoperative endocrine therapy (type of endocrine therapy), LR (ipsilateral breast) and LRR (ipsilateral breast, axillary lymph nodes, internal mammary lymph nodes, supraclavicular or infraclavicular lymph nodes), date of diagnosis of LR or LRR, time to LR or LRR, date of death due to any cause, and time to last follow-up.

Outcomes

The outcomes of interest were the occurrence of LR and/or LRR. LR was defined as disease recurrence in the ipsilateral breast. LRR was defined as disease recurrence in the ipsilateral breast or axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. All instances of LR and LRR were considered events, regardless of whether they were the initial site of disease recurrence or followed the identification of a distant metastasis.

Statistical Analysis

We combined all individual participant data into a single meta-analytic model (ie, a 1-stage approach). To account for heterogeneity between different cohorts, all models included a categorical variable named study (with 9 categories, 1 for each of the 9 cohorts included).

The rates of missing values from potential predictors for LR or LRR ranged from 0% to 96%. Variables with > 50% missing values (HER2 status, presence of lymphovascular invasion, Ki-67, morphology of residual tumor, and surgical margin status) were excluded. Missing data were imputed for the variables with <50% missing values (menopausal status, age, preoperative T classification, preoperative N classification, ER status, PR status, pCR [breast only and breast and axilla], pathologic complete response in axilla [pN0], and number of positive lymph nodes postoperatively). The imputation was performed within each cohort using the chained equations method. For each cohort, 10 multiple imputed data sets were created and used for the analyses. Two studies did not provide data regarding menopausal status,[19,22] 2 did not provide data regarding preoperative N classification,[20,21] and 1 study did not provide data regarding pCR.[17] To assign values for these missing data, we performed multiple imputations using all relevant potential predictive factors from the pooled data set using the same method. Information was available for 100% and 89%, respectively, of LRs and LRRs.

We used survival analysis to estimate prognostic factors that predict the 10-year risk of LR or LRR. We censored analyses at the date of death, last available follow-up, or 10 years after diagnosis.

We used Cox regression to calculate the unadjusted hazard ratios (HRs) for each potential predictor. Any variables associated with the development of LR or LRR during follow-up on bivariate analysis (with a cutoff α of .10) were considered for entry into the multivariable models. We used log-minus-log plots to check that the proportional hazards assumption was met before undertaking Cox proportional hazards multivariable regression. Multivariable models were built using backward elimination of variables.

We assigned a score of 1 to the variable with the lowest regression coefficient. The scores for the remaining variables were obtained by dividing their regression coefficient by the coefficient of the variable with the lowest regression coefficient and then rounding to the nearest integer. We used Kaplan-Meier plots and the log-rank test to assess the separation achieved by prognostic models in different cutoff values.

We internally validated our model by performing the bootstrap procedure (1000 iterations). Discrimination of the model, which is expressed as a concordance (C) statistic, indicates to what extent the model distinguishes between patients with or without LR or LRR during follow-up. The C statistic has a theoretical range of between 0.5 and 1.0, but typically ranges from 0.60 to 0.85 for prognostic models. Different cutoff values for each model were tested to identify the cutoff value with higher discriminatory ability.

Sensitivity analyses were performed using all patients and excluding data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) cohort[23] because the NSABP contributed greater than one-half of the total pooled patient database. We performed an additional sensitivity analysis by performing complete case analysis as a method with which to handle missing values. Finally, we performed a sensitivity analysis using the Fine-Gray competing risk method to estimate the predictors of LR or LRR, with death as a competing risk.[24] Due to a lack of information regarding the presence of distant metastasis, we could not include distant metastasis as a competing risk.

All statistical analyses were performed using SPSS statistical software (version 20.0; IBM Corporation, Armonk, New York).

TABLE 1. Characteristics of Cohort Studies Included in the Pooled Data Set

Study	Country	Enrollment Period	No. of Patients	Median Age (Range), Years	T3 to T4 Disease at Diagnosis No. (%)	N + at Diagnosis, No. (%)	ER Negative No. (%)	pCR, No. (%)	Median Follow-Up, Months	LR Rate (95% CI), %	LRR Rate (95% CI), %
Ishitobi 2012[15]	Japan	1995-2009	374	48 (18-76)	70 (18.7)	190 (50.8)	177 (47.3)	61 (16.3)	47.8	4.8 (3.1-7.5)	10.4 (7.6-14.1)
Mamounas 2012[16]	United States	1988-1993 and 1995-2000	1905	48 (25-79)	263 (13.8)	767 (40.3)	340 (17.8)	474 (24.9)	184.8 and 128.4	8.7 (7.5-10.0)	11.0 (9.7-12.5)
Matsuda 2014[17]	Japan	2001-2008	520	49 (26-76)	66 (12.7)	69 (13.3)	108 (20.8)	-	51	1.7 (1.0-3.4)	11.9 (9.4-15.0)
Tiezzi 2008[18]	Brazil	1990-2003	86	50.5 (27-83)	59 (68.6)	36 (41.9)	17 (19.8)	7 (8.1)	61.3	9.3 (4.4-18.0)	9.3 (4.4-18.0)
Cebrecos 2010[19]	Spain	1996-2007	120	54 (30-83)	27 (22.5)	28 (23.3)	35 (29.2)	37 (30.8)	35	5.0 (2.1-11.0)	5.0 (2.1-11.0)
Fitzal 2011[20]	Austria	1995-2007	187	50 (26-74)	50 (26.7)	-	128 (68.4)	12 (6.4)	60	7.0 (3.9-11.9)	7.0 (3.9-11.9)
Angelucci 2013[21]	Italy	1999-2011	210	49 (25-78)	24 (11.4)	-	65 (31)	4 (1.9)	42.1	5.2 (2.8-9.4)	5.2 (2.8-9.4)
Shin 2013[22]	South Korea	2004-2007	71	45 (29-68)	24 (33.8)	71 (100)	36 (50.7)	9 (12.7)	66.9	9.9 (4.4-19.8)	9.9 (4.4-19.8)
Mittendorf 2013[23]	United States	1987-2005	652	50.5 (26-84)	94 (14.4)	156 (23.9)	311 (47.7)	94 (14.4)	86.4	10.3 (8.1-12.9)	10.3 (8.1-12.9)

Abbreviations: 95% CI, 95% confidence interval; ER, estrogen receptor; LR, local disease recurrence; LRR, locoregional disease recurrence; pCR, pathologic complete remission.

TABLE 2. Multivariable Cox Proportional Regression Analysis of Predictive Factors for 10-Year Risk of LR

Predictive Factor	β	*P*	HR	95% CI	Points
ER-negative disease	0.631	<.001	1.890	1.462-2.431	2
LNs positive preoperatively	0.319	.013	1.374	1.065-1.765	1
Absence of pN0	0.428	.003	1.534	1.169-2.013	1
>3 positive LNs	0.471	0.003	1.683	1.204-2.354	1

Abbreviations: 95% CI, 95% confidence interval; ER, estrogen receptor; HR, hazard ratio; LN, lymph node; LR, local disease recurrence; pN0, pathologic complete response in axilla.

RESULTS

Characteristics of the 9 cohorts included in the pooled analysis are shown in Table 1. In total, 4170 patients from 9 cohorts were eligible for the pooled analysis. After the exclusion of 45 patients who did not receive radiotherapy after surgery, 4125 patients remained eligible for the analyses.

In total, 268 of 4125 patients (6.5%; 95% confidence interval [95% CI], 5.8%-7.3%) developed LR within 10 years from diagnosis whereas 387 of 3770 patients (10.3%; 95% CI, 9.3%-11.3%) developed LRR.

Risk Factors for LR

Table 2 shows the results from the multivariable Cox proportional regression model for 10-year risk for LR. Four factors were found to be independently associated with a higher risk of LR: 1) the presence of ER-negative disease; 2) the presence of positive lymph nodes before NCT; 3) the absence of pN0 after NCT; and 4) the presence of >3 positive lymph nodes postoperatively. The C statistic of the final model was 0.772. The bootstrap-corrected C statistic was 0.742.

All analyses were repeated using the complete case method to handle missing values, and similar results were found. In addition, all analyses were repeated after excluding the NSABP cohort, and the same variables remained statistically significant for LR. A sensitivity analysis using the competing risk model, with death as competing risk, gave comparable HRs for the 4 prognostic factors.

An integer-based score intended for clinical use was developed based on the Cox regression model (Table 2). The score was used to identify 3 risk groups: a low-risk group, an intermediate-risk group, and a high-risk group. The low-risk group included individuals with ≤ 1 points. The 10-year risk of LR in this group was 4.0% (95% CI, 3.1%-5.0%). The intermediate-risk group consisted of patients with 2 to 4 points with a 10-year LR risk of 7.9% (95% CI, 6.8%-9.1%). The high-risk group included

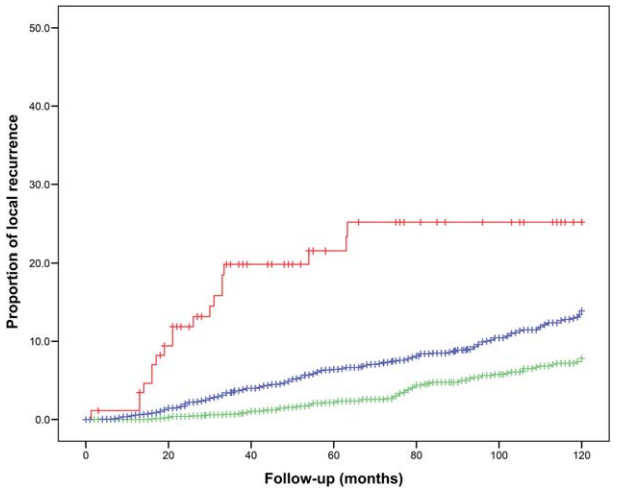

Figure 2. Kaplan-Meier curves for 10-year local disease recurrence risk in all patients according to prognostic risk group. Green line indicates the low-risk group (0-1 points); blue line, intermediate-risk group (2-4 points); red line, high-risk group (5 points).

individuals with 5 points with a 10-year risk of LR of 20.4% (95% CI, 13.1%-30.3%). The C statistic of the integer-based score was 0.758. Figure 2 shows Kaplan-Meier curves for the separation of the prognostic score into low-risk, intermediate-risk, and high-risk groups based on the 10-year LR risk (log-rank test for the comparison, $P<.001$).

Risk Factors for LRR

Table 3 shows the results from the multivariable Cox proportional regression model for 10-year risk of LRR. Six factors were found to be associated with an increased risk of LRR: 1) the presence of ER-negative disease; 2) T3 to T4 tumor at the time of diagnosis; 3) the presence of positive lymph node(s) before NCT; 4) the absence of pCR in the breast after NCT; 5) the absence of pN0 after NCT; and 6) the presence of >3 pathologically positive lymph nodes identified in the axillary lymph node dissection specimen. The C statistic of the final model was 0.770. The bootstrap-corrected C statistic was 0.740.

The same sensitivity analysis described for the LR model was performed for LRR. Neither the use of the complete case method nor the exclusion of the NSABP cohort altered the results. In addition, the competing risk model revealed comparable HRs for the prognostic risk factors.

The patients were stratified into 3 risk categories according to the LRR prognostic risk score: a low-risk group with 0 to 2 points (LRR rate, 3.2%; 95% CI, 2.1%-4.8%), the intermediate-risk group with 3 to 6 points (LRR rate, 10.1%; 95% CI, 8.7%-11.8%), and the high-risk group with 7 to 10 points (LRR rate, 24.1%; 95% CI, 16.9%-33.1%) (Table 3). The C statistic for the score was 0.736. Figure 3 shows Kaplan-Meier curves for the separation of the prognostic score into low-risk, intermediate-risk, and high-risk groups based on the 10-year LRR risk (log-rank test for the comparison, $P<.001$).

TABLE 3. Multivariable Cox Proportional Regression Analysis of Predictive Factors for 10-Year Risk of LRR

Predictive Factor	β	*P*	HR	95% CI	Points
cT3-T4 disease	0.491	<.001	1.643	1.284-2.102	2
ER-negative disease	0.527	<.001	1.802	1.425-2.279	2
LNs positive preoperatively	0.292	.009	1.335	1.089-1.648	1
Absence of breast pCR	0.329	.016	1.390	1.069-1.807	1
Absence of pN0	0.529	<.001	1.697	1.350-2.137	2
>3 positive LNs	0.714	<0.001	2.041	1.564-2.662	2

Abbreviations: 95% CI, 95% confidence interval; ER, estrogen receptor; HR, hazard ratio; LN, lymph node; LRR, locoregional disease recurrence; pCR, pathologic complete response; pN0, pathologic complete response in lymph nodes.

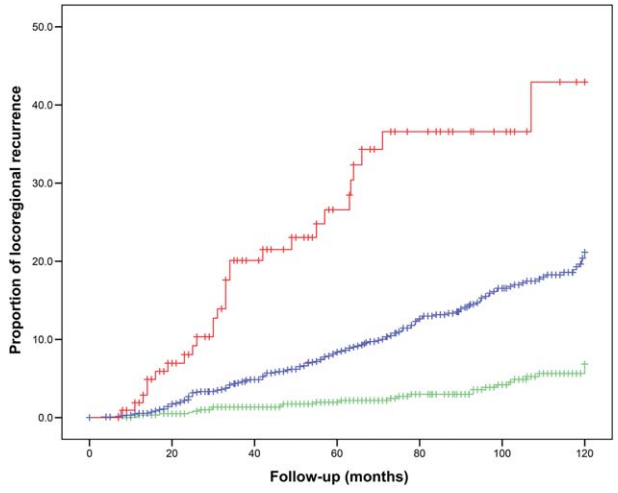

Figure 3. Kaplan-Meier curves for 10-year locoregional disease recurrence risk in all patients according to prognostic risk group. Green line indicates the low-risk group (0-2 points); blue line, intermediate-risk group (3-6 points); red line, high-risk group (7-10 points).

DISCUSSION

Based on individual patient data from 9 different cohorts, we were able to investigate the risk of LR and LRR in a large cohort of >4000 patients. The data allowed us to develop 2 clinical scores that predict the risk of a patient with breast cancer developing LR and LRR, respectively,

after NCT and BCT. There were 4 factors found to be associated with both LR and LRR: 1) the presence of ER-negative disease; 2) the presence of positive lymph nodes at the time of diagnosis; 3) residual positive lymph nodes after NCT; and 4) >3 pathologically positive lymph nodes. Two additional factors were found to be associated with LRR: 1) clinical/radiologic T3 to T4 tumor at the time of diagnosis; and 2) the presence of residual disease in the breast after NCT. These factors divided the patients into risk categories with significant differences in LR and LRR rates. It is important to note that the pooled rates of LR and LRR for the entire cohort were relatively low, an observation that confirmed the oncological safety of BCS after NCT in a large percentage of patients with breast cancer.

The risk factors identified in the current analysis as being predictive of the risk of LR and LRR have been described previously.[14-17] For example, the presence of residual disease after NCT in the breast and axilla has been associated not only with higher rates of LR and LRR but also with higher mortality.[7] However, this analysis aimed to quantify all these risk factors in easy-to-use clinical scores using a pooled patient cohort in an effort to overcome the limitations of previous studies, including small sample size and the use of single-institution data that make the generalizability of results questionable.

The current study has several strengths. First, the large sample size of >4000 patients allowed for the performance of multivariable analyses using all the available potential predictive factors without the need to shrink the regression coefficients. Furthermore, the results proved to be robust when sensitivity analyses were performed to test the potential risk of bias due to the fact that the largest cohort in the data set herein accounted for approximately 46% of the pooled data set or due to the use of the multiple imputation method to handle missing values. In addition, the pooled data set included data from several institutions worldwide, which we believe enhances the generalizability of these results. Finally, the clinical scores are easy to use in clinical practice because they are based on a set of tumor characteristics that always are available to clinicians before and after surgery.

The current study also had some limitations that should be taken into account when interpreting the results. First, some potentially interesting predictors of LRR from previous efforts to develop risk scores for LRR after NCT and BCT[14-17] were excluded from the analyses due to the lack of sufficient data. However, none of the excluded factors was found to be an independent predictor in all 4 previously published risk scores; residual pathologic tumor size >2 cm[14] and tumor grade[17] each were found to be independent predictors in 1 risk score, whereas lymphovascular invasion[14,17] and residual tumor morphology[14,15] were predictors in 2 risk scores. Another potential risk factor that could not be tested due to the lack of eligible data was surgical margin status, a problem that is anticipated in a relatively high percentage of patients who undergo BCS after NCT.[25] Second, the models in the current study did not take into account the molecular subtype of the tumors (except for ER and PR status) due to a paucity of data regarding HER2 and HER2-directed therapy. Previous studies have suggested that patients with triple-negative breast cancer are at an increased risk of LRR after NCT and BCT.[26,27] The current study results confirm the pivotal role of ER status in the risk of LR and LRR. The potential role of HER2 status and the therapeutic effect of trastuzumab on the risk of LR or LRR in this setting could not be determined in this pooled data set because the majority of patients included were treated before the routine use of trastuzumab for patients with HER2-positive disease. Prior studies have shown that HER2 positivity appears to be associated with a higher risk of LR or LRR after NCT and BCS; however, this association is less pronounced than the one observed with regard to ER negativity.[26-29] Another limitation was the fact that some eligible cohorts were not included in the pooled data set because the primary investigators did not provide us with individual patient data. The addition of these cohorts would increase the pooled data set by nearly 1400 additional patients. However, the current study sample size of >4000 patients was large enough for multivariable analyses. Finally, despite the fact that our internal validation based on the bootstrap procedure demonstrated that the models were stable, an external validation of the models is lacking.[30] Further studies are needed to validate the scores and, if possible, improve their discriminatory ability though the incorporation of other potentially predictive factors such as molecular subtype.

The proposed clinical scores, based on tumor characteristics that are available in clinical practice, could aid clinicians in counseling patients with breast cancer who are receiving NCT with regard to locoregional therapy options. Some of the predictive factors can be determined only after surgery is performed and, as a result, the clinical scores will not be available for surgical planning. However, the scores may be used to identify patients at high risk of either LR or LRR after surgery who may be considered for more aggressive approaches in radiotherapy planning (eg, boost) or for participation in clinical trials evaluating novel strategies for LR control. Considering

the previously suggested association between LR and LRR and the risk of distant breast cancer recurrence and mortality,[31-33] it can be expected that the proposed clinical scores from the current analysis might be prognostic for mortality as well. Further studies are needed to investigate this hypothesis.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Antonios Valachis: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Eleftherios P. Mamounas**: Data curation, investigation, and writing–review and editing. **Elizabeth A. Mittendorf**: Data curation, investigation, and writing–review and editing. **Naoki Hayashi**: Data curation, investigation, and writing–review and editing. **Makoto Ishitobi**: Data curation, investigation, and writing–review and editing. **Clara Natoli**: Data curation, investigation, and writing–review and editing. **Florian Fitzal**: Data curation, investigation, and writing–review and editing. **Isabel T. Rubio**: Data curation, investigation, and writing–review and editing. **Daniel G. Tiezzi**: Data curation, investigation, and writing–review and editing. **Hee-Chul Shin**: Data curation, investigation, and writing–review and editing. **Stewart J. Anderson**: Data curation and writing–review and editing. **Kelly K. Hunt**: Data curation, investigation, and writing–review and editing. **Naoko Matsuda**: Data curation, investigation, and writing–review and editing. **Shozo Ohsumi**: Data curation, investigation, and writing–review and editing. **Athina Totomi**: Data curation, project administration, validation, and writing–review and editing. **Cecilia Nilsson**: Conceptualization, methodology, supervision, validation, and writing–review and editing.

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