Long-term overall survival of patients who undergo breast-conserving therapy or mastectomy for early operable HER2-Positive breast cancer after preoperative systemic therapy: an observational cohort study

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Summary

Background Understanding the survival outcomes associated with breast-conserving therapy (BCT) and mastectomy after preoperative systemic therapy (PST) enables clinicians to provide more personalized treatment recommendations. However, lack of firm survival benefit data limits the breast surgery choices of human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients who receive PST. We sought to determine whether BCT or mastectomy after PST for early operable HER2-positive breast cancer is associated with better long-term survival outcomes and determine the degree to which PST response affects this association.

Methods In this observational cohort study, we compared the long-term survival outcomes of BCT and mastectomy after PST for HER2-positive breast cancer and evaluated the impact of PST response on the relationship between breast surgery performed and survival outcomes. Our cohort included 625 patients with early operable HER2-positive breast cancer who received PST followed by BCT or mastectomy between January 1998 and October 2009. These patients also received standard postoperative radiation, trastuzumab, and endocrine therapy as indicated clinically. We used propensity score matching to assemble mastectomy and BCT cohorts with similar baseline characteristics and used Kaplan–Meier plots and Cox proportional hazards regression to detect associations between surgery types and outcomes. Furthermore, in this study, we analyzed the original data of 625 patients using the inverse probability of treatment weighting (IPTW) method to enhance the reliability of the comparison between the mastectomy and BCT cohorts by addressing potential confounding variables.

Findings Propensity score matching yielded cohorts of 221 patients who received BCT and 221 patients who underwent mastectomy. At the median follow-up time of 9.9 years, compared with BCT, mastectomy was associated with worse overall survival (hazard ratio, 1.66; 95% confidence interval [CI]: 1.08–2.57; $P = 0.02$). In patients who had axillary lymph node pathological complete response, mastectomy was associated with worse overall survival before matching (hazard ratio, 2.17; 95% CI: 1.22–3.86; $P < 0.01$) and after matching (hazard ratio, 2.12; 95% CI: 1.15–3.89; $P = 0.02$). Among patients with pathological complete response in the breast, the survival results did not differ significantly between BCT and mastectomy patients. IPTW method validated that BCT offers better overall survival in patients who had axillary lymph node pathological complete response.

Interpretation People with HER2-positive breast cancer who have already had PST are more likely to survive after BCT, especially if they get a pathological complete response in the axillary lymph nodes. These findings underscore the necessity for further investigation into how responses to PST can inform the choice of surgical intervention and the potential impact on overall survival. Such insights could lead to the development of innovative tools that support personalized surgical strategies in the management of breast cancer.

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Keywords: Breast-conserving therapy; Mastectomy; HER2-Positive breast cancer; Long-term survival; Pathological complete response

Research in context

Evidence before this study

We conducted a search across PubMed, Web of Science, and Google Scholar databases to collate data on survival outcomes in breast cancer patients who underwent mastectomy or breast-conserving therapy (BCT). The search criteria encompassed articles that contained the terms "breast cancer" or "breast carcinoma" in conjunction with "mastectomy" or "breast-conserving therapy" or "BCT", and included any of the terms "survival", "overall survival," or "OS". This review was specifically focused on studies published between January 1, 2021 and April 30, 2023 that included female breast cancer patients who had completed breast surgery. No restrictions were placed on the languages of publications. From this search, 30 studies were identified. The majority of the studies indicated a superior survival outcome associated with BCT as compared to mastectomy in patients with early-stage breast cancer. Nevertheless, two studies reported no significant statistical difference in survival outcomes between the BCT and mastectomy cohorts. It is noteworthy that advancements in preoperative systemic therapy (PST) for breast cancer have progressively enhanced the probability of achieving a pathological complete response. Currently, PST represents the established standard for the management of locally advanced breast cancer. However, there is a paucity of research evaluating the long-term survival outcomes of patients who receive BCT or mastectomy following PST. Specifically, studies are scarce that focus on patients achieving a pathological complete response in the axillary lymph nodes and/or breast after PST.

Added value of this study

In our longitudinal cohort study, we observed that patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer who achieved pathological complete response in the axillary lymph nodes following PST exhibited significantly superior overall survival when treated with BCT compared to those who undergo mastectomy.

Implications of all the available evidence

The findings from our study contribute valuable insights for surgical planning following PST. They indicate that for patients with HER2-positive breast cancer who demonstrate a radiological complete response in the axillary lymph nodes using advanced breast imaging, BCT can be considered a viable option, provided there are no contraindications.

Introduction

Breast-conserving therapy (BCT; lumpectomy followed by whole-breast moderate-dose radiotherapy) and mastectomy are the two primary types of breast cancer removal surgery. Lumpectomy is an operation in which a woman has a lump such as a tumor removed from one of her breasts, rather than having the whole breast removed which is defined as mastectomy. Types of mastectomy in modern breast surgery include modified radical mastectomy, simple mastectomy, skin-sparing mastectomy, and nipple-areolar-sparing mastectomy. BCT results in acceptable cosmetic outcomes and, compared with mastectomy, better physical and psychological well-being[1]; fewer postoperative complications, such as lymphedema, chest numbness; and improved quality of life. In addition, whole-breast moderate-dose radiotherapy eliminates potential breast micro metastatic disease and alters the tumor microenvironment to favor the activation of the immune infiltrate.[2]

For patients with locally advanced breast cancer, especially human epidermal growth factor receptor 2 (HER2)-positive breast cancer, the standard of care includes preoperative systemic therapy (PST) nowadays, which is intended to reduce the risk of distant recurrence, downstage the extent of disease in the breast and/or regional lymph nodes, and provide information to predict response to adjuvant therapies.[3] The results of recent clinical trials suggest that newer HER2-targeting agents enhance the sensitivity of HER2-positive breast cancer to preoperative chemotherapy and result in significantly higher rates of pathological complete response, which is generally associated with a higher use of BCT.[4,5]

However, the breast surgical management of patients who receive PST is complicated.[6] A prior study revealed that removing residual lesions, as opposed to the primary tumor, does not impact the recurrence rate in individuals undergoing BCT after PST.[7] Although numerous studies found that overall survival rates are

comparable, recent observational studies suggested that initial BCT may be associated with better 10-year survival than mastectomy, which is partly attributable to the improvements in breast imaging, pathological margin assessment, systemic therapy, and radiotherapy.[8–10] However, the optimal breast surgical approach for many HER2-positive breast cancer patients achieving a pathological complete response following PST remains uncertain since the better survival results of BCT was based on adjuvant populations.

So far, there has not been enough research that looks at whether BCT or mastectomy is better for long-term survival in HER2-positive breast cancer patients after PST, especially for those who get a pathological complete response in the axillary lymph nodes and/or breast tissue. The study's goals are to find out how the type of breast surgery (BCT or mastectomy) a patient has affects their chance of survival and to see how PST-induced responses affect the relationship between breast surgery choices and patient overall survival.

Methods

Study design and participants

This observational cohort study was conducted in accordance with the Declaration of Helsinki and approved by MD Anderson's Institutional Review Board (IRB). IRB waived the requirement to obtain individual informed consent. We searched MD Anderson's electronic medical records and tumor registry system and identified 2448 consecutive women diagnosed with early-stage HER2-positive breast cancer between January 1998 and October 2009. Among these patients, 951 patients were not amenable to upfront resection of breast cancers or expected to undergo surgery after PST, and these patients were further selected according to the inclusion and exclusion criteria in our study. Eligible patients were age 18 years or older, had histologically confirmed primary HER2-positive breast cancer, had known estrogen receptor (ER) status, and received chemotherapy with or without anti-HER2 therapy followed by mastectomy or BCT. HER2 positivity was defined as a score of 3+ on immunohistochemical analysis or as positive results on fluorescence in situ hybridization. All patients had breast carcinoma of the early stages [breast Tumor stage 1–T3, axillary lymph Node stage 0–N3, and without distant Metastases (0) disease] based on the seventh edition of the American Joint Committee on Cancer Staging System. A flow chart of patient selection is given in Supplementary Figure S1. The final analysis included 625 patients. This study follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (Supplementary S1 Checklist).

Procedures

All patients underwent only one surgery after PST and BCT patients received postoperative moderate-dose radiation to the whole breast in our study. Patients also received standard postoperative adjuvant radiation, trastuzumab, and endocrine therapy as clinically indicated. These BCT patients with high-risk factors as referenced in mastectomy patients had also received axillary lymph nodes dissection and postoperative adjuvant radiation to the regional lymph node region, which employed the same postoperative adjuvant radiation criteria and indication as mastectomy patients. Two trained physicians (X.H. and A.Q.) reviewed the patients' medical records and extracted clinicopathological information, survival information, and treatment information. Two senior physician investigators (S.-C.J.Y. and X.H.) checked the final data and resolved ambiguous data.

Outcomes

Pathological complete response was defined as the absence of any invasive cancer in the breast and lymph nodes after preoperative systemic therapy, with the exception of residual ductal carcinoma in situ. Breast complete response (BCR) was defined as no residual invasive cancer in the breast. Lymph node complete response (LCR) was defined as no residual invasive cancer in the axillary lymph nodes. Overall survival was defined as the time from the date of breast cancer diagnosis to the date of death from any cause or last follow-up. Patients alive or lost to follow-up were censored at the date they were last known to be alive. Patients were followed until June 30, 2018. The longest follow-up time was 20 years.

Statistical analysis

Because certain baseline characteristics can influence the choice of surgery type following PST for HER2-positive breast cancer, we used propensity score matching to create cohorts of mastectomy patients and BCT patients whose distributions of such baseline characteristics were similar. We use the model-based variance estimator from the maximum partial likelihood estimator for the Cox proportional hazards model in the matched analysis. Using nearest neighbor propensity score matching and the R package "MatchIt", a total of 442 patients with HER2-positive breast cancer were chosen. The criteria used for matching included age, tumor stage, BCR, LCR, PST regimen (which included preoperative systemic therapy and/or postoperative trastuzumab treatment), postoperative adjuvant endocrine therapy, and postoperative adjuvant radiation therapy (which includes the radiation field surrounding the regional lymph node region and/or chest wall, as opposed to the moderate-dose radiotherapy to the entire breast in BCT). These factors may have an impact on the type of surgery that is chosen in clinical practice, as well as significant variables in single variable statistical analysis in our analysis. The demographic data, tumor characteristics, and treatment-related variables of these matched cohorts were

compared using the Pearson chi-square test. In the matched cohorts, adjustment for the comparative risk of overall survival was accomplished with the use of a Cox proportional hazards regression model that was stratified on the matched pair to preserve the benefit of matching. We also used propensity score matching to create cohorts of LCR and BCR patients matched according to tumor stage, PST regimen, age, postoperative adjuvant endocrine therapy and postoperative adjuvant radiation therapy. The Kaplan–Meier method was used to calculate overall survival rates according to breast surgery type and other prognostic factors. The log-rank test was used to identify significant differences between groups. Multivariable Cox proportional hazard models with adjustment for significant prognostic factors in the univariable analysis were used to identify associations between breast surgery types and survival outcomes among patients who had LCR or BCR. We also employed univariable and multivariable Cox proportional hazard models to ascertain the relationship between different types of breast surgery and survival outcomes across all patients. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. And the proportional hazards assumption was test and Schoenfeld individual test p values were >0.05. To validate the robustness of our findings, we conducted an analysis using inverse probability of treatment weighting (IPTW). All statistical analyses were done using SPSS 22.0 (IBM Corporation, Armonk, NY, USA) and R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/). *P* values of less than 0.05 were considered significant.

Roles of the funding source

The study funders had no role in the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit for publication. No pharmaceutical company nor other agency were involved in this study, and this research received no specific grant funding, with any role of the funding source in this work. The corresponding authors had full access to the data and have final responsibility for publication.

Results

Patients

The characteristics of all 625 patients by surgery type before and after matching are shown in Table 1. Of these patients, 221 (221/625, 35.4%) underwent BCT and 404 (404/625, 64.6%) underwent mastectomy. Before matching, 260 (260/625, 41.6%) had pathological complete response and 365 (365/625, 58.4%) had residual disease. The median follow-up time for all 625 patients was 9.6 years (interquartile range, 5.8–12.8 years). Propensity score matching yielded BCT and mastectomy cohorts with 221 patients each. These cohorts had identical numbers of patients with stage I or II disease or with stage III disease; with or without LCR after matching; with or without postoperative adjuvant endocrine therapy, and menopause status. Distributions of ER status, nuclear grade, with or without trastuzumab as part of PST; age at diagnosis; with or without postoperative adjuvant radiotherapy, and with or without BCR after PST did not differ significantly between the matched cohorts.

Survival outcomes for matched cohorts

At the median follow-up time of 9.9 years, the overall survival rate of the BCT patients (86.0%; 95% CI: 81.3%–90.8%) was significantly higher than that of the mastectomy patients (79.3%; 95% CI: 72.8%–84.5%) ($P = 0.02$) (Fig. 1). The results of the univariable and multivariable analyses for overall survival after matching are given in Table 2. In the univariable analysis, BCR ($P < 0.01$), LCR ($P < 0.01$), and chemotherapy with trastuzumab ($P < 0.01$) were associated with better overall survival, whereas mastectomy ($P = 0.02$) was associated with worse overall survival. The surgery type, BCR, LCR, age at diagnosis, PST regimens, and disease stage were adjusted for in the multivariable analysis. In the multivariable analysis, BCR (hazard ratio, 0.48; 95% CI: 0.29–0.81; $P < 0.01$), LCR (hazard ratio, 0.49; 95% CI: 0.31–0.78; $P < 0.01$), and chemotherapy with trastuzumab (hazard ratio, 0.50; 95% CI: 0.30–0.84; $P = 0.01$) were associated with better overall survival, whereas mastectomy (hazard ratio, 1.62; 95% CI: 1.05–2.51; $P = 0.03$) was associated with worse overall survival. Age at diagnosis and disease stage were not significantly associated with overall survival.

Survival outcomes for LCR and BCR cohorts

To evaluate the effect of surgery type on the survival outcomes of patients who had LCR or BCR after PST, we performed propensity score matching of the LCR and BCR populations. Among both patients who had LCR and patients who had BCR, those who received BCT had significantly better overall survival than those who underwent mastectomy ($P = 0.02$ and 0.03, respectively) (Fig. 2A and B). The characteristics of the patients who had LCR after PST by surgery type before and after matching are given in Supplementary Table S1. After matching, the BCT and mastectomy groups' distributions of disease stage, nuclear grade, BCR status, PST regimen, and postoperative adjuvant radiation therapy did not differ significantly ($P = 0.70$, 0.57, 0.14, 0.74, and 0.44, respectively).

The results of the multivariable analyses for overall survival among patients who had LCR or BCR before and after matching are given in Table 3. For patients who had LCR, mastectomy was an independent negative prognostic factor for overall survival both before matching (hazard ratio, 2.17; 95% CI: 1.22–3.86; $P < 0.01$) and after matching (hazard ratio, 2.12; 95% CI: 1.15–3.89; $P = 0.02$). For patients who had BCR, neither BCT nor mastectomy was associated with overall survival before or after matching.

Characteristic	Before PSM					After PSM[a]				
	BCT, n = 221		Mastectomy, n = 404		P	BCT, n = 221		Mastectomy, n = 221		P
PST response, n (%)					0.07					0.51
Non-pCR	118	(53.4)	247	(61.1)		118	(53.4)	110	(49.8)	
pCR	103	(46.6)	157	(38.9)		103	(46.6)	111	(50.2)	
BCR, n (%)					0.18					0.63
No	110	(49.8)	225	(55.7)		110	(49.8)	104	(47.1)	
Yes	111	(50.2)	179	(44.3)		111	(50.2)	117	(52.9)	
LCR, n (%)					<0.01					0.91
No	50	(22.6)	154	(38.1)		50	(22.6)	48	(21.7)	
Yes	171	(77.4)	250	(61.9)		171	(77.4)	173	(78.3)	
Age, n (%)					0.01					0.39
<50 years	101	(45.7)	229	(56.7)		101	(45.7)	111	(50.2)	
≥50 years	120	(54.3)	175	(43.3)		120	(54.3)	110	(49.8)	
Menopause status, n (%)					0.24					0.96
Premenopausal	100	(45.2)	211	(52.2)		100	(45.2)	97	(43.1)	
Postmenopausal	120	(54.3)	191	(47.3)		120	(54.3)	123	(55.7)	
Unknown	1	(0.5)	2	(0.5)		1	(0.5)	1	(0.5)	
PST, n (%)					0.81					0.45
Chemotherapy without trastuzumab	102	(46.2)	192	(47.5)		102	(46.2)	111	(50.2)	
Chemotherapy with trastuzumab	119	(53.8)	212	(52.5)		119	(53.8)	110	(49.8)	
Nuclear grade, n (%)					0.60					0.33
I or II	42	(19.0)	86	(21.3)		42	(19.0)	51	(23.1)	
III	178	(80.5)	314	(77.7)		178	(80.5)	167	(75.6)	
Unknown	1	(0.5)	4	(1.0)		1	(0.5)	3	(1.4)	
Adjuvant endocrine therapy					0.51					>0.99
No	119	(53.8)	205	(50.7)		119	(53.8)	120	(54.3)	
Yes	102	(46.2)	199	(49.3)		102	(46.2)	101	(45.7)	
ER status, n (%)					0.02					0.18
Negative	115	(52.0)	170	(42.1)		115	(52.0)	100	(45.2)	
Positive	106	(48.0)	234	(57.9)		106	(48.0)	121	(54.8)	
Disease stage, n (%)					<0.01					>0.99
I or II	173	(78.3)	266	(65.8)		173	(78.3)	173	(78.3)	
III	48	(21.7)	138	(34.2)		48	(21.7)	48	(21.7)	
Postoperative adjuvant radiation therapy n (%)					<0.01					0.57
No	115	(52.0)	155	(38.4)		115	(52.0)	108	(48.9)	
Yes	106	(48.0)	249	(61.6)		106	(48.0)	113	(51.1)	

BCT, breast-conserving therapy; PST, preoperative systemic therapy; pCR, pathological complete response; BCR, breast complete response; LCR, lymph node complete response; ER, estrogen receptor. [a]Matching variables were disease stage, BCR, LCR, PST regimen, age, adjuvant endocrine therapy, and adjuvant radiation therapy.

Table 1: **Characteristics of patients by surgery type before and after propensity score matching (PSM).**

Survival outcomes for the entire cohort

The results of the univariable and multivariable analyses for the overall survival of all patients are given in Table 4. In the univariable analyses, compared with mastectomy patients, BCT patients had significantly higher rates of 10-year overall survival (hazard ratio, 2.05; 95% CI: 1.39–3.02; $P < 0.01$). In the multivariable analysis, mastectomy (hazard ratio, 1.69; 95% CI: 1.14–2.51; $P < 0.01$) was associated with worse overall survival, whereas BCR (hazard ratio, 0.54; 95% CI: 0.35–0.83; $P < 0.01$), LCR (hazard ratio, 0.48; 95% CI: 0.32–0.72; $P < 0.01$), and chemotherapy with trastuzumab (hazard ratio, 0.56; 95% CI: 0.38–0.81; $P < 0.01$) were associated with better overall survival. Age at diagnosis and disease stage had no significant association with overall survival. In the inverse probability of treatment weighting analysis of all patients with HER2-positive breast cancer who received PST, the hazard ratio for mastectomy was 1.89 (95% CI: 1.26–2.86; $P < 0.01$). The inverse probability of treatment weighting analysis also showed that BCT was associated with better overall survival in the entire cohort of patients with HER2-positive breast cancer and in patients who had LCR or BCR (Supplementary Figure S2A–C).

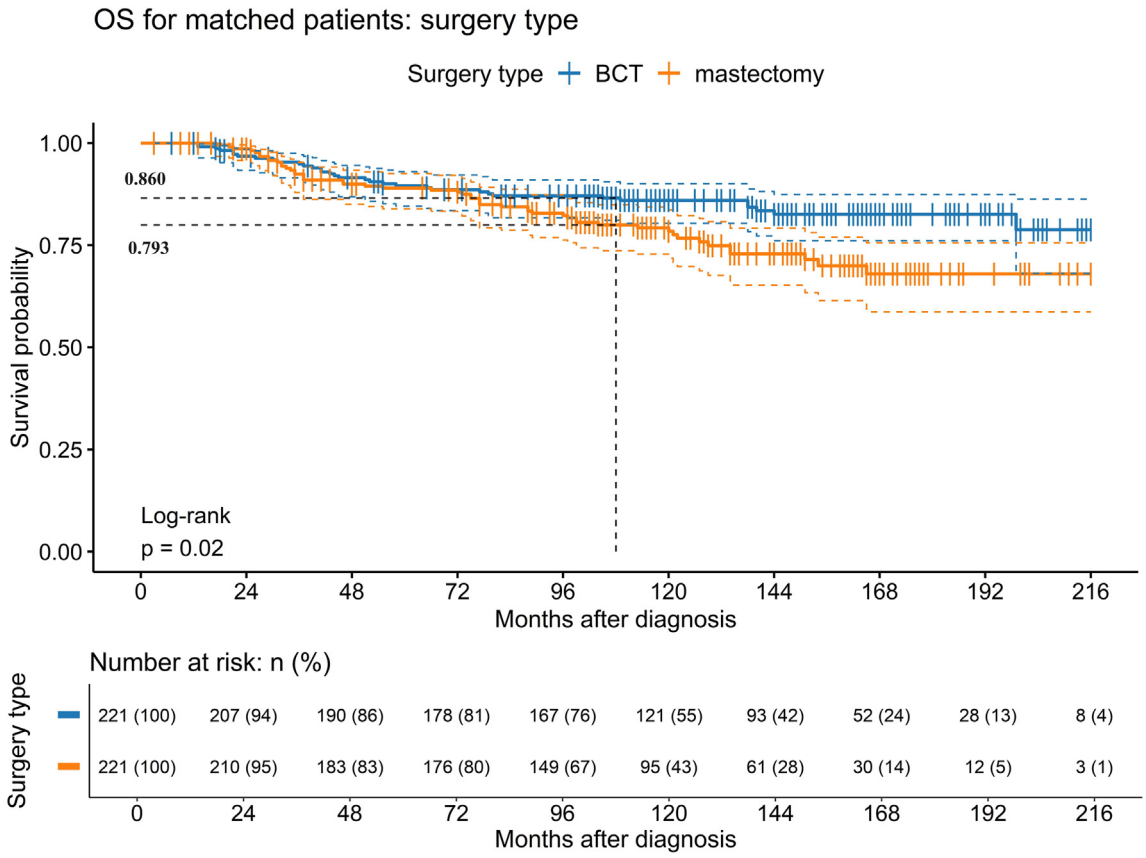

Fig. 1: **Survival outcomes of matched patients who underwent breast-conserving therapy or mastectomy.** Overall survival (OS) of matched patients by surgery type. The vertical dotted line represents the median follow-up time.

Discussion

We found that, when PST response was not taken into account, BCT after PST was associated with better overall survival than mastectomy. When PST response was taken into account, BCT offered a significant survival benefit over mastectomy for patients who had LCR after PST but not for those who had BCR after PST. While the sample sizes in subgroup analyses were small, the lack of a statistically significant difference between BCT and mastectomy within the BCR subgroup does not mean that there is no true difference because of inadequate statistical power. Our results represent the most dependable data available to discern whether BCT or mastectomy provides superior overall survival for individuals undergoing PST. Additionally, our findings contribute to understanding the association between breast surgery type and survival outcomes in patients experiencing LCR after PST. The findings of the present study should help improve the selection of patients for BCT and provide more insight into breast surgery choice. In addition, the response to PST can have important implications for the choice of surgery in patients with early operable disease.

Our finding that BCT patients had better survival outcomes than mastectomy patients is contrary to the traditional consensus that BCT and mastectomy yield similar survival outcomes. Our findings are in agreement with those of Agarwal et al.,[11] who also demonstrated that BCT patients have better survival outcomes than mastectomy patients. In previous studies of patients receiving BCT after PST, pathological complete response and LCR were associated with lower risks of all-cause mortality, locoregional recurrence, and distant metastasis.[12,13] These findings are in accordance with those of our study, which demonstrated that LCR can confer a survival benefit in patients with HER2-positive breast cancer. Moreover, the mechanism of the finding that BCT offered a significant survival benefit over mastectomy for patients who had lymph node complete response after PST needs to be explored further. In this study, we focused on breast surgical options after PST and compared the overall survival of BCT and mastectomy patients with or without receipt of postoperative adjuvant radiation to the regional lymph node region and/or chest wall. The factors of postoperative

Covariate	Univariable analysis			Multivariable analysis		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Breast surgery (n)						
BCT (221)						
Mastectomy (221)	1.66	(1.08–2.57)	0.02	1.62	(1.05–2.51)	0.03
BCR (n)						
No (214)						
Yes (228)	0.30	(0.19–0.49)	<0.01	0.48	(0.29–0.81)	<0.01
LCR (n)						
No (98)						
Yes (344)	0.31	(0.20–0.47)	<0.01	0.49	(0.31–0.78)	<0.01
Age (n)						
<50 years (212)						
≥50 years (230)	1.29	(0.84–1.98)	0.25	1.36	(0.88–2.09)	0.17
PST (n)						
Chemotherapy without trastuzumab (213)						
Chemotherapy with trastuzumab (229)	0.33	(0.20–0.53)	<0.01	0.50	(0.30–0.84)	0.01
Nuclear grade (n)						
I or II (93)						
III (345)	1.29	(0.74–2.26)	0.37			
ER status (n)						
Negative (215)						
Positive (227)	1.02	(0.67–1.56)	0.92			
Postoperative adjuvant radiation therapy						
No						
Yes	1.42	(0.92–2.17)	0.11			
Disease stage						
I or II (346)						
III (96)	1.22	(0.47–1.44)	0.49	1.11	(0.51–1.60)	0.73

HR, hazard ratio; CI, confidence interval; BCT, breast-conserving therapy; BCR, breast complete response; LCR, lymph node complete response; PST, preoperative systemic therapy; ER, estrogen receptor. The surgery type, BCR, LCR, age at diagnosis, PST regimens, and disease stage were adjusted for in the multivariable analysis.

Table 2: **Results of univariable and multivariable analyses for overall survival after propensity score matching.**

adjuvant radiation, systemic therapy and stage in both cohorts were well balanced using propensity score matching method. The LCR minimized the impact of potential residual disease in lymph node on the outcomes. Our data suggest that whole-breast moderate-dose radiotherapy was one of the major factors that contributed to the better survival outcomes of patients who received BCT after PST. A previous study showed that moderate-dose radiation to the breast, compared with mastectomy, had a better potential to release neoantigens to activate an antitumoral immune response in patients with high tumor burden[14,15] Therefore, the better survival outcomes of LCR patients who received BCT may be attributed to the transformative impact of radiotherapy on the primary breast tumor microenvironment, encompassing the expression of new molecules, release of neoantigens, and enhancement of original receptors in immune and tumor cells.[16–18] We speculate that a more extensive surgery like mastectomy depresses the immune response to breast cancer cells. However, the complex relationship among surgical trauma, medical treatment, moderate-dose radiation to the breast, and immune response remains largely unknown.

Kuerer et al.[19] recently reported that surgery might be omitted in patients with an exceptional response to PST and standard whole-breast radiotherapy. In our study, if the primary gross tumor has disappeared after PST, radiotherapy primarily targeting surrounding breast microscopic disease might lead to minimal benefits in patients experiencing BCR.[20] Wrubel et al.,[21] who reported findings similar to ours, suggested that improved systemic therapy options combined with the locoregional control provided by radiotherapy with tangential axillary exposure may contribute to the survival benefit. The role of postoperative breast radiation in eliminating micrometastases, potentially shed or spread during surgery, becomes more comprehensible in this context. Radiation, recognized for its potent induction of apoptosis in tumor cells,[22] and it exhibits the capacity to augment antitumor immunity. Another study showed

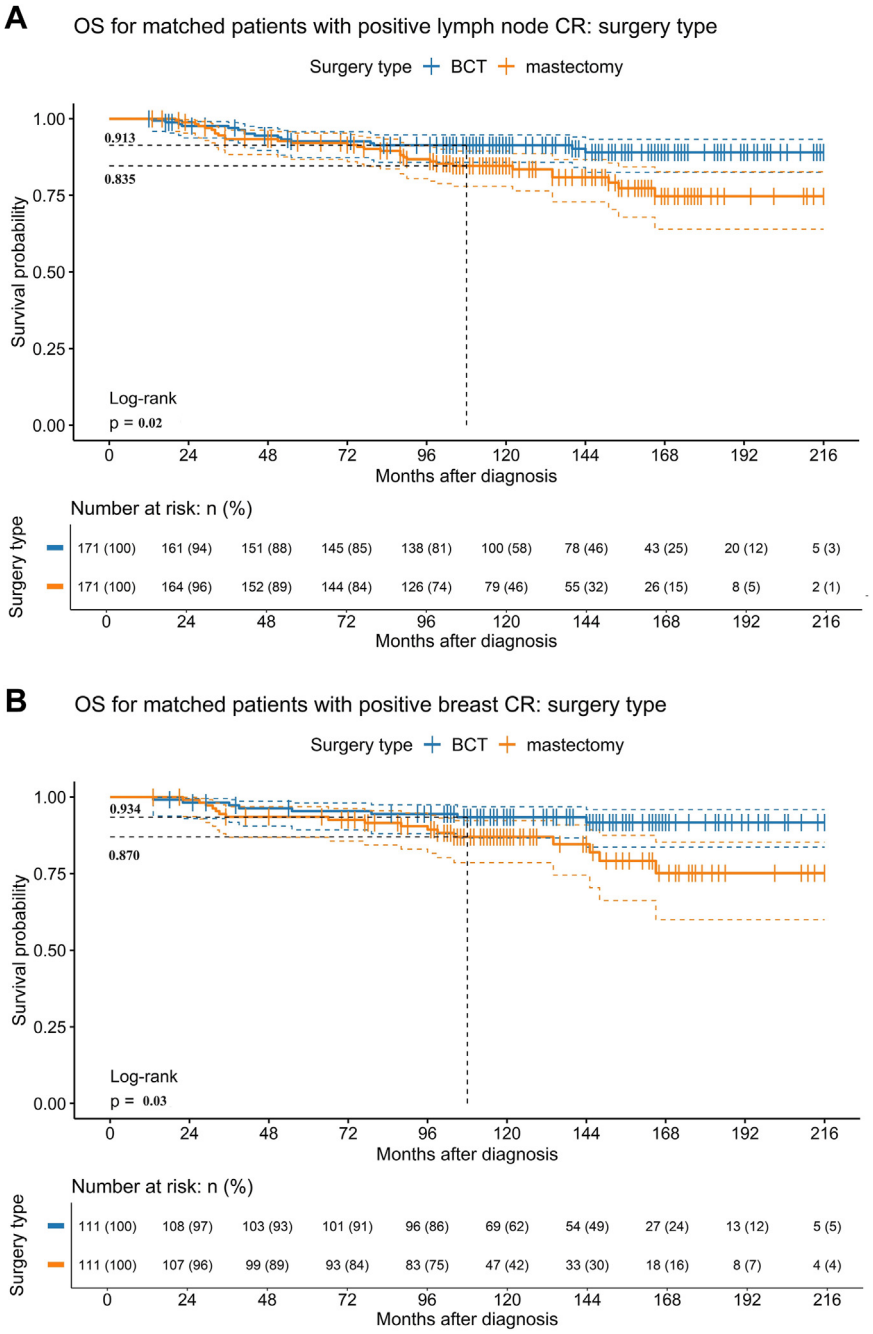

***Fig. 2:* Survival outcomes of matched patients who had lymph node complete response or breast complete response following preoperative systemic therapy and who underwent breast-conserving therapy or mastectomy.** A. Overall survival (OS) of matched patients with lymph node complete response after preoperative systemic therapy (PST) by surgery type. B. OS of matched patients with breast complete response after PST by surgery type. The vertical dotted line represents the median follow-up time.

that tumors from patients who received preoperative chemotherapy had a distinct B-cell subset with B-cell–dependent anti-tumor immunity.[23] Further research is needed to determine the mechanism underlying the greater survival benefit of BCT.

Whether residual disease is present in lymph nodes after PST is a vital determinant of outcomes.[24] To precisely evaluate PST response, other researchers investigated the use of core or fine-needle biopsy combined with imaging, which had false negative rates ranging

Results	LCR group		BCR group	
	HR (95% CI)	P	HR (95% CI)	P
After matching[a]				
BCT	Reference		Reference	
Mastectomy	2.12 (1.15–3.89)	0.02	1.74 (0.60–5.02)	0.31
Before matching				
BCT	Reference		Reference	
Mastectomy	2.17 (1.22–3.86)	<0.01	2.00 (0.83–4.85)	0.13

Note: Matching variables in patients with LCR were disease stage, BCR, PST regimen, age, and adjuvant endocrine therapy; Matching variables in patients with BCR were disease stage, LCR, PST regimen, age, adjuvant endocrine therapy, and adjuvant radiation therapy. After matching, Multivariable adjusted factors in patients with LCR were BCR and surgery type; Multivariable adjusted factors in patients with BCR were surgery type and radiotherapy; which were significantly associated with OS in the univariate analysis. Before matching, Multivariable adjusted factors in patients with LCR were BCR and surgery type; Multivariable adjusted factors in patients with BCR were LCR, surgery type and radiotherapy; which were significantly associated with OS in the univariate analysis. HR, hazard ratio; CI, confidence interval; BCT, breast-conserving therapy. [a]After matching, in the LCR group, the BCT and mastectomy cohorts each included 171 patients; and in the BCR group, the BCT and mastectomy cohorts each included 111 patients.

Table 3: **Results of the multivariable analyses for overall survival (OS) among patients who had lymph node complete response (LCR) or breast complete response (BCR) before and after propensity score matching (PSM).**

from 37% to 50%.[25,26] However, noninvasive technologies based on molecular imaging with advanced antibody conjugated probes and potentially artificial intelligence, radiomics, and convolutional neural networks may pave a new way for the future.[27]

Few studies have analyzed the factors that are potentially associated with long-term overall survival, particularly surgery type, in HER2-positive breast cancer patients who receive PST. In our study, overall survival was the primary endpoint because most aging breast cancer survivors face an increasing risk of morbidity and mortality from cardiovascular disease, and breast cancer and cardiovascular disease share some risk factors.[28,29] In addition, chemotherapy and anti-HER2 therapy can induce cardiotoxicity.[30] Effective radiotherapy and systemic therapy have probably reduced the incidence of local recurrence. Previous studies showed that anti-HER2 therapy can decrease the rate of locoregional recurrence.[31] The unprecedented survival results of the ISPY-2 trial implied that a pathological complete response after PST might reduce the recurrence rate by 80%, even in patients with HER2-positive breast cancer.[32] Tumor size, node positivity, HER2-positive disease, and triple-negative disease all have been reported to be associated with the successful downstaging of ineligible patients to BCT.[30] Several clinical trials, including the NeoSphere,[33] Peony,[34] KRISTINE,[35] and TRAIN-2 trials,[36] have confirmed the benefits of using dual or multiple anti-HER2 therapies in the preoperative setting for patients with HER2-positive breast cancer, but few trials have focused on the breast surgical management of these patients. Our results also demonstrate that the addition of anti-HER2 therapy to chemotherapy conveys a long-term survival benefit in patients with HER2-positive breast cancer who received PST regardless of age, hormone receptor status, or tumor stage.

This study has inherent limitations. Firstly, the ethnic characteristic of the study population was missing. While it was an observational cohort study with a comprehensive long-term follow-up, the accuracy of overall survival data was ensured, and the low rate of loss to follow-up at MD Anderson Cancer Center strengthens data reliability. However, the non-randomized observational design represents a limitation. Initially varying distributions of age at diagnosis, ER status, postoperative adjuvant radiation therapy status, and disease stage between the BCT and mastectomy groups were addressed through propensity score matching to mitigate selection bias, and these covariates were further considered in the multivariable analysis. In addition, our study sample was not large enough to perfectly match by different postoperative adjuvant radiation dose/fractionation; the possible effect of different postoperative adjuvant radiation dose/fractionation in our study was not included in our study. Moreover, locally advanced disease did not have a negative effect on survival outcomes, possibly because of the small number of patients who had it. Because the combination of pertuzumab and trastuzumab results in higher pathological complete response rate compared to trastuzumab alone does, the use of both monoclonal antibodies is currently the standard of care in the preoperative setting.[37] The effect of BCT in patients treated with pertuzumab and trastuzumab requires further investigation. Also, for patients who do not have pathological complete response after PST, adjuvant trastuzumab emtansine (T-DM1) therapy can offer a clinical benefit.[38] Moreover, the BCR subgroup did not experience many events sufficient to detect statistical significance of any BCT protective hazard. Additional studies with larger cohorts would be necessary to evaluate the effects of novel HER2-targeted therapies on survival patient outcomes in the preoperative setting.

In conclusion, our data suggest that for patients with HER2-positive breast cancer, BCT following PST is associated with improved overall survival compared to mastectomy. This improvement is also observed in patients exhibiting a complete response in the axillary lymph nodes post-PST. More research is needed to confirm that making surgical decisions based on radiological responses after PST is a good way to predict what will happen in this group of patients and to learn more about the molecular processes that give patients who get a complete lymph node response a better chance of overall survival.

Covariate	Univariable analysis		Multivariable analysis		
	10-year OS, % (95% CI)	*P*	HR	95% CI	*P*
Breast surgery (n)		<0.01			
BCT (221)	86.0 (81.3–90.8)		1.0 [reference]		
Mastectomy (404)	72.9 (68.3–77.9)		1.69	1.14–2.51	<0.01
BCR (n)		<0.01			
No (335)	68.2 (63.0–73.8)		1.0 [reference]		
Yes (290)	88.6 (84.8–92.5)		0.54	0.35–0.83	<0.01
LCR (n)		<0.01			
No (204)	57.8 (50.7–65.8)		1.0 [reference]		
Yes (421)	87.2 (83.9–90.6)		0.48	0.32–0.72	<0.01
Age (n)		0.50			
<50 years (330)	77.6 (72.8–82.6)		1.0 [reference]		
≥50 years (295)	78.0 (73.1–83.2)		1.19	0.85–1.65	0.31
PST (n)		<0.01			
Chemotherapy without trastuzumab (294)	68.0 (62.5–73.9)		1.0 [reference]		
Chemotherapy with trastuzumab (331)	87.4 (83.7–91.2)		0.56	0.38–0.81	<0.01
Nuclear grade (n)		0.80			
I/II (74)	80.6 (73.6–88.3)				
III (256)	77.1 (73.2–81.2)				
Postoperative adjuvant radiation therapy		<0.01			
No	84.1 (79.6–88.9)		1.0 [reference]		
Yes	72.8 (68.0–78.0)		1.15	0.78–1.70	0.49
ER status (n)		0.80			
Negative (285)	77.4 (72.4–82.7)				
Positive (340)	78.0 (73.4–83.0)				
Disease stage (n)		0.90			
I/II (439)	77.6 (73.5–81.8)		1.0 [reference]		
III (186)	78.2 (71.9–85.1)		1.01	0.68–1.49	0.80

HR, hazard ratio; CI, confidence interval; BCT, breast-conserving therapy; BCR, breast complete response; LCR, lymph node complete response; PST, preoperative systemic therapy; ER, estrogen receptor.

Table 4: **Results of univariable and multivariable analyses for overall survival (OS) for the entire cohort.**

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Data sharing statement

Upon reasonable request and provided all ethical and legal requirements are met, the original data presented in the study will be made available by the authors, without undue reservation.

Declaration of interests

Sai-Ching Jim Yeung participated in an expert panel discussion for Salix Pharmaceuticals. Francisco J. Esteva had received consulting fees from Genzyme Corporation, Novartis, AstraZeneca, Stemline, and Genentech. The other authors declare no competing interests relevant to this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100712.

References

1 Hanson SE, Lei X, Roubaud MS, et al. Long-term quality of Life in patients with breast cancer after breast conservation vs mastectomy and reconstruction. *JAMA Surg.* 2022;157(6):e220631. https://doi.org/10.1001/jamasurg.2022.0631.

2 Rodriguez-Ruiz ME, Vitale I, Harrington KJ, Melero I, Galluzzi L. Immunological impact of cell death signaling driven by radiation on the tumor microenvironment. *Nat Immunol.* 2020;21(2):120–134.

3 Asselain B, Barlow W, Bartlett J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol.* 2018;19(1):27–39.

4 Criscitiello C, Golshan M, Barry WT, et al. Impact of neoadjuvant chemotherapy and pathological complete response on eligibility for breast-conserving surgery in patients with early breast cancer: a meta-analysis. *Eur J Cancer.* 2018;97:1–6.

5 Masuda N, Toi M, Yamamoto N, et al. Efficacy and safety of trastuzumab, lapatinib, and paclitaxel neoadjuvant treatment with or without prolonged exposure to anti-HER2 therapy, and with or without hormone therapy for HER2-positive primary breast cancer: a randomised, five-arm, multicentre, open-label phase II trial. *Breast Cancer.* 2018;25(4):407–415.

6 Kim HJ, Dominici L, Rosenberg SM, et al. Surgical treatment after neoadjuvant systemic therapy in young women with breast cancer: results from a prospective cohort study. *Ann Surg*. 2022;276(1):173–179.
7 Shin HC, Han W, Moon HG, et al. Breast-conserving surgery after tumor downstaging by neoadjuvant chemotherapy is oncologically safe for stage III breast cancer patients. *Ann Surg Oncol*. 2013;20(8):2582–2589.
8 Chu QD, Hsieh M-C, Lyons JM, Wu X-C. 10-Year survival after breast-conserving surgery compared with mastectomy in Louisiana women with early-stage breast cancer: a population-based study. *J Am Coll Surg*. 2021;232(4):607–621.
9 Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MM. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173,797 patients. *BMJ*. 2015;351:h4901. https://doi.org/10.1136/bmj.h4901.
10 Royce TJ, Gupta GP, Marks LB. Breast conservation therapy versus mastectomy for breast cancer. *Lancet Oncol*. 2020;21(4):492–493.
11 Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. *JAMA Surg*. 2014;149(3):267–274.
12 Zhang J, Lu C-Y, Chen H-M, Wu S-Y. Pathologic response rates for breast cancer stages as a predictor of outcomes in patients receiving neoadjuvant chemotherapy followed by breast-conserving surgery. *Surg Oncol*. 2021;36:91–98.
13 Valachis A, Mamounas EP, Mittendorf EA, et al. 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. *Cancer*. 2018;124(14):2923–2930.
14 Martinez-Zubiaurre I, Chalmers AJ, Hellevik T. Radiation-induced transformation of immunoregulatory networks in the tumor stroma. *Front Immunol*. 2018;9:1679. https://doi.org/10.3389/fimmu.2018.01679.
15 Younes AI, Barsoumian HB, Sezen D, et al. Addition of TLR9 agonist immunotherapy to radiation improves systemic antitumor activity. *Transl Oncol*. 2021;14(2):100983. https://doi.org/10.1016/j.tranon.2020.100983.
16 Liu Q, Hao Y, Du R, et al. Radiotherapy programs neutrophils to an antitumor phenotype by inducing mesenchymal-epithelial transition. *Transl Lung Cancer Res*. 2021;10(3):1424–1443.
17 Ozpiskin OM, Zhang L, Li JJ. Immune targets in the tumor microenvironment treated by radiotherapy. *Theranostics*. 2019;9(5):1215–1231.
18 Lan Y, Moustafa M, Knoll M, et al. Simultaneous targeting of TGF-β/PD-L1 synergizes with radiotherapy by reprogramming the tumor microenvironment to overcome immune evasion. *Cancer Cell*. 2021;39(10):1388–1403.
19 Kuerer HM, Smith BD, Krishnamurthy S, et al. Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2022;23(12):1517–1524.
20 Cho WK, Park W, Choi DH, et al. Is tumor bed boost necessary in patients who achieved pathological complete response following neoadjuvant chemotherapy and breast conserving therapy? (KROG 12-05 and 16-16). *Breast*. 2019;45:43–47.
21 Wrubel E, Natwick R, Wright GP. Breast-conserving therapy is associated with improved survival compared with mastectomy for early-stage breast cancer: a propensity score matched comparison using the national cancer database. *Ann Surg Oncol*. 2021;28(2):914–919.
22 Ye LF, Chaudhary KR, Zandkarimi F, et al. Radiation-induced lipid peroxidation triggers ferroptosis and synergizes with ferroptosis inducers. *ACS Chem Biol*. 2020;15(2):469–484.
23 Lu Y, Zhao Q, Liao J-Y, et al. Complement signals determine opposite effects of B cells in chemotherapy-induced immunity. *Cell*. 2020;180(6):1081–1097.
24 Ma Y, Zhu M, Lv M, Yuan P, Chen X, Liu Z. Impact of residual disease biomarkers on the prognosis of HER2-positive breast cancer following neoadjuvant therapy. *Cancer Med*. 2023;12(10):11293–11304.
25 Li Y, Zhou Y, Mao F, et al. The diagnostic performance of minimally invasive biopsy in predicting breast pathological complete response after neoadjuvant systemic therapy in breast cancer: a meta-analysis. *Front Oncol*. 2020;10:933. https://doi.org/10.3389/fonc.2020.00933.
26 Vriens BE, de Vries B, Lobbes MB, et al. Ultrasound is at least as good as magnetic resonance imaging in predicting tumour size post-neoadjuvant chemotherapy in breast cancer. *Eur J Cancer*. 2016;52:67–76.
27 Liu Z, Li Z, Qu J, et al. Radiomics of multiparametric MRI for pretreatment prediction of pathologic complete response to neoadjuvant chemotherapy in breast cancer: a multicenter study. *Clin Cancer Res*. 2019;25(12):3538–3547.
28 Strongman H, Gadd S, Matthews A, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. *Lancet*. 2019;394(10203):1041–1054.
29 He X, Ji J, Dai X, et al. Association of cardiovascular disease risk factors with late cardiotoxicity and survival in HER2-positive breast cancer survivors. *Clin Cancer Res*. 2021;27(19):5343–5352.
30 Petruolo O, Sevilimedu V, Montagna G, Le T, Morrow M, Barrio A. How often does modern neoadjuvant chemotherapy downstage patients to breast-conserving surgery? *Ann Surg Oncol*. 2020;28(1):287–294.
31 Bellon JR, Guo H, Barry WT, et al. Local-regional recurrence in women with small node-negative, HER2-positive breast cancer: results from a prospective multi-institutional study (the APT trial). *Breast Cancer Res Treat*. 2019;176(2):303–310.
32 Yee D, DeMichele AM, Yau C, et al. Association of event-free and distant recurrence–free survival with individual-level pathologic complete response in neoadjuvant treatment of stages 2 and 3 breast cancer: three-year follow-up analysis for the I-SPY2 adaptively randomized clinical trial. *JAMA Oncol*. 2020;6(9):1355–1362.
33 Gianni L, Pienkowski T, Im Y-H, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791–800.
34 Shao Z, Pang D, Yang H, et al. Efficacy, safety, and tolerability of pertuzumab, trastuzumab, and docetaxel for patients with early or locally advanced ERBB2-positive breast cancer in Asia: the PEONY phase 3 randomized clinical trial. *JAMA Oncol*. 2019;6(3):e193692. https://doi.org/10.1001/jamaoncol.2019.3692.
35 Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2018;19(1):115–126.
36 van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(12):1630–1640.
37 Hatschek T, Foukakis T, Bjöhle J, et al. Neoadjuvant trastuzumab, pertuzumab, and docetaxel vs trastuzumab emtansine in patients with ERBB2-positive breast cancer: a phase 2 randomized clinical trial. *JAMA Oncol*. 2021;7(9):1360–1367.
38 Mamounas EP, Untch M, Mano MS, et al. Adjuvant T-DM1 versus trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analyses from KATHERINE. *Ann Oncol*. 2021;32(8):1005–1014.