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ORIGINAL ARTICLE – BREAST ONCOLOGY

Survival Outcomes for Patients With Clinical Complete Response After Neoadjuvant Chemotherapy: Is Omitting Surgery an Option?

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ABSTRACT

Background. Surgery after neoadjuvant chemotherapy (NCT) is an accepted treatment approach for locally advanced and some early-stage breast cancers, even for patients with a clinical complete response (cCR) after NCT. This study sought to evaluate the survival outcomes for patients with cCR to NCT who did not undergo surgery.

Methods. The National Cancer Data Base (NCDB) was used to identify 93,417 women age 18 years or older with a diagnosis of invasive breast cancer who received NCT between 2010 and 2015. The study identified 350 women with cT1-4, N0-3, and M0 tumors who underwent NCT and did not have surgery. A matched surgical cohort was extracted from the NCDB, and overall survival (OS) was compared between the surgical and nonsurgical patients after NCT.

Results. Of the 350 NCT patients who did not undergo surgery, 45 (12.9%) had cCR, 51 (14.6%) had a partial response, 241 (68.9%) had a response but whether complete or partial was not recorded, and 13 (3.7%) had no response/progression. The 5-year OS was better in the cCR group than in the no-cCR group (96.8% vs 69.8%; $p = 0.004$). A 5-year OS analysis of the cCR patients without surgery ($n = 45$; median follow-up period, 37 months) compared with the patients with a pathologic complete response who underwent surgery ($n = 3938$; median follow-up period, 43 months) showed no statistically significant difference (96.8% vs 92.5%, respectively; $p = 0.15$).

Conclusion. This retrospective cohort study demonstrated that active surveillance or de-escalation therapy may be an option for patients who achieve cCR. Prospective studies are underway to determine whether a subgroup of patients may forgo surgery in the setting of cCR after NCT.

Neoadjuvant chemotherapy (NCT) can reduce the extent of surgery for both the breast and the axilla.[1] In the last decade, NCT was widely used not only for locally advanced breast cancer, but also for some early-stage breast cancer patients with biologically aggressive subtypes such as triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2-positive (HER2 +) disease that normally would need adjuvant chemotherapy.

Findings have shown that NCT increases breast-conservation therapy (BCT) rates without a reduction in overall survival (OS) or an increased risk of local recurrence.[2–4] Furthermore, NCT allows physicians to monitor in vivo efficacy of the treatment, and it also is used as a surrogate clinical end point for long-term survival when a pathologic complete response (pCR) is achieved.[5]

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Developments of new drugs and treatment combinations have increased the rates of response, and pCR is achieved for up to 60% of patients, especially those with HER2 + and TNBC subtypes.[6–8] These increased pCR rates have led to studies about omitting surgery for a select subgroup of patients who have high concordance between clinical complete response (cCR), which is evaluated before definitive surgery, and pCR, which is evaluated after surgery as a final pathology report.

Early attempts to omit surgery and administer radiotherapy after a cCR date back to late 1970s.[4–9] However, due to high local–regional recurrence (LRR) rates, this treatment approach was put aside.[4] In the modern era, higher cCR rates concordant with pCR rates and developments of highly sensitive and specific imaging methods and biopsy techniques have revived the idea of obviating local therapy. Very few patients undergo no surgery after NCT. The reason for no surgery usually is the patient's preference, but sometimes it could be the physician's choice due to accompanying comorbidities. Because data are limited concerning patients with cCR after NCT who did not undergo surgery, we sought to evaluate the survival outcomes for these patients using the National Cancer Data Base (NCDB).

METHODS

Patient Cohort

Using the NCDB, we identified 93,417 women 18 years of age or older who had a diagnosis of invasive breast cancer and received NCT between 2010 and 2015. To demonstrate the effect of NCT on survival, we extracted two different cohorts (nonsurgical and surgical cohorts) depending on the inclusion and exclusion criteria further defined.

For our nonsurgical cohort, the study excluded patients who had undergone surgery, patients who received neoadjuvant endocrine therapy, patients with clinical or pathologic Stage 4 cancer as defined by the American Joint Committee on Cancer (AJCC) 7th edition, patients with more than one cancer during a lifetime, patients with in situ carcinoma in histology, and patients with unknown or missing survival data. To define our nonsurgical cohort further, we excluded patients with discordant (i.e., no surgery mentioned but pathologic stage given) or missing data related to our inclusion criteria.

Our final nonsurgical cohort included 350 patients (Fig. 1). We divided our nonsurgical cohort into two groups (cCR and non-cCR) for further analysis. Uni- and multivariate analyses to demonstrate association with cCR were performed.

For our surgical cohort, patients who underwent surgery after NCT were included. All the remaining exclusion criteria for the nonsurgical cohort also applied to this group. Our final surgical cohort included 33,326 patients.

In the NCDB, complete response is defined as no residual tumor after completion of NCT. Partial response is defined as residual tumor after completion of NCT but not larger than the initial status of the tumor. Response is defined as a response to NCT without the type of response being defined as a complete or partial response after completion of NCT. No response (NR) is defined as stable disease or progression of the tumor after completion of NCT. Furthermore, if the patient did not undergo surgery, response to NCT is defined as a clinical response as stated in physician's notes. But if the patient underwent surgery, response to NCT is defined as a pathologic response because NCDB does not present the clinical response after NCT if the patient had surgery. Therefore, cCR will hereafter define complete response for patients without surgery, and pCR will define complete response for patients with surgery.

Statistical Analysis

To assess differences in categorical and continuous variables, Pearson's Chi square, independent samples *t* test, and one-way analysis of variance (ANOVA) were performed. Variables related to cCR with *p* values lower than 0.10 in the univariable analysis were entered into a multivariable binary logistic regression model. Overall survival was defined as the time from diagnosis to death or last contact with the patient, at which point the patient was right censored.

Although response to NCT in NCDB was divided into four groups (cCR, clinical partial response [cPR], clinical response [cR], and NR), we divided the nonsurgical cohort into two groups as mentioned earlier. Differences between categorical and continuous variables were calculated between the cCR and no-cCR groups. Kaplan–Meier survival curves were used to illustrate OS differences for the entire nonsurgical cohort and subgroups. Log-rank tests with *p* values lower than 0.05 were considered statistically significant. Finally, to determine whether OS differed between the nonsurgical cCR cohort and the surgical pCR cohort after NCT, we performed a Kaplan–Meier survival analysis comparing these two complete responder groups.

The NCDB gives only OS, not the disease-free survival of patients. To account for this limitation, we examined the Charlson-Deyo comorbidity scores of the patients. This scoring system presents the 10-year estimated survival of the patient depending on 15 major comorbidities.[10] In the NCDB output, it is classified as scores 0, 1, 2, and $\geq$ 3. The estimated 10-year survival rate according to the Charlson/

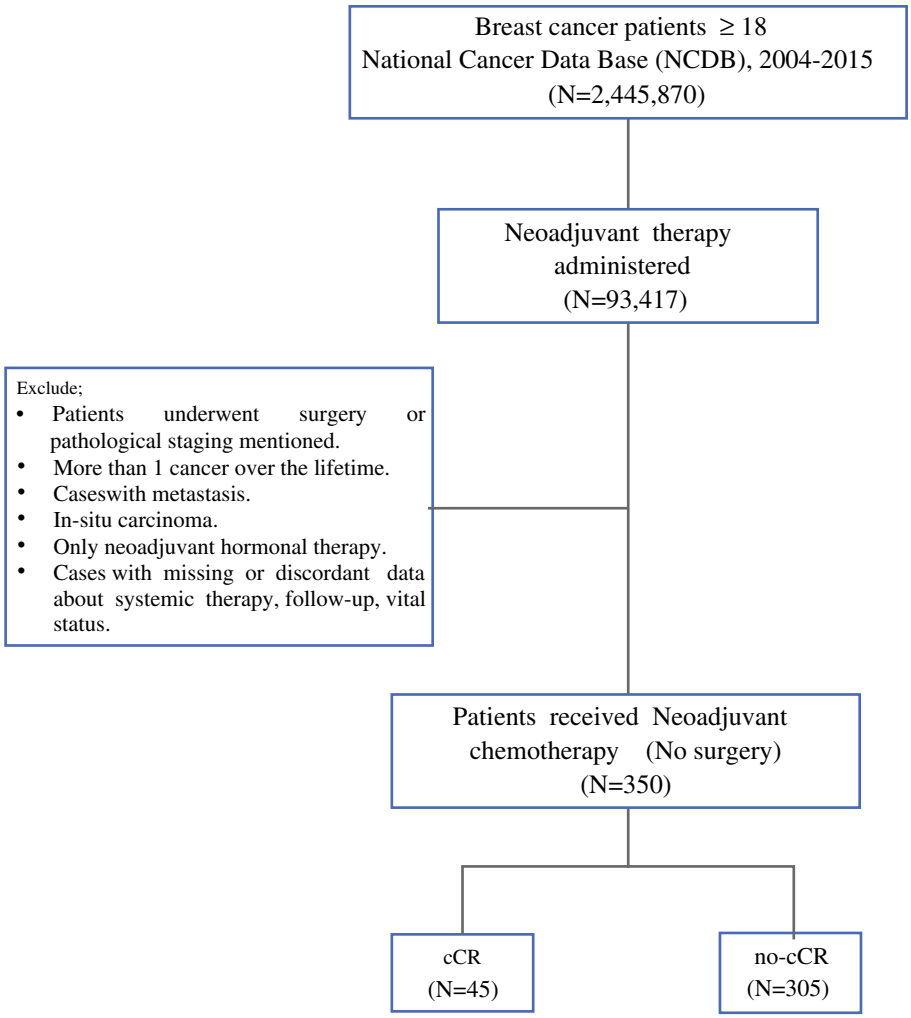

FIG. 1 Flow diagram for breast cancer patients who received neoadjuvant chemotherapy not followed by surgery; National Cancer Data Base (NCDB) 2004–2015. cCR, clinical complete response

Deyo comorbidity score is 98% for score 0, 96% for score 1, 90% for score 2, and ≤ 77% for score ≥ 3. Statistical analysis was performed using SPSS version 24.0 (released 2016 as IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA).

RESULTS

We identified 350 breast cancer patients who received NCT but did not undergo surgery (Fig. 1). The demographics and clinic-pathologic features of these patients are summarized in Table 1. The median follow-up time was 30 months. Of the 350 patients, 45 (12.9%) had cCR, 51 (14.6%) had cPR, 241 (68.9%) had cR, and 13 (3.7%) had NR. The cCR and no-cCR groups did not exhibit any statistically significant demographic differences. The Charlson-Deyo comorbidity score was lower than 2 for 334 (95.4%) of the patients (100% for cCR vs 94.8% for no-cCR; $p = 0.45$).

The patients in the cCR group had smaller tumor sizes (T1–T2) than the no-cCR group (36 [80%] of 45 of cCR vs 162 [53.8%] of 305 for no-cCR; $p < 0.001$). In contrast, nodal involvement was more frequent in the cCR group (91.1% [$n = 41$] for cCR vs 68.5% [$n = 209$] for no-cCR; $p < 0.001$).

The AJCC 7th edition clinical staging did not differ between the two groups. The histologic subtype was invasive ductal carcinoma for 90% ($n = 315$) of the non-surgical cohort. Luminal, HER2 +, and TNBC were well-balanced between the cCR and no-cCR groups ($p = 0.53$) (Table 1). The cCR rates for receptor subgroups were 9.8% for HR +/HER2–, 11.1% for HR +/HER2 +, 17.6% for HR–/HER2 +, and 12.8% for HR–/HER2–.

TABLE 1 Demographic, clinic, and pathologic characteristics of breast cancer patients who received neoadjuvant chemotherapy

Variables	No-surgery cohort				Surgery cohort			
	All patients	Response to neoadjuvant chemotherapy		*P* Value	All patients	Response to neoadjuvant chemotherapy		*P* Value
	N = 350 (100%) *n* (%)	Clinical CR *N* = 45 (12.9%) *n* (%)	Non-clinical CR *N* = 305 (87.1%) *n* (%)		*N* = 33,326 (100%) *n* (%)	Pathologic CR *N* = 3938 (11.8%) *n* (%)	Non-pathologic CR *N* = 29,388 (88.2%) *n* (%)	
Median age (23–90 years)	54 (23–88)	54 (33–79)	54 (23–88)	0.9	52 (18–90)	50 (20–90)	52 (18–90)	<0.001
Median follow-up (3–156 months)	30 (1–80)	37 (15–80)	29 (1–75)	<0.001	37 (1–86)	43 (3–85)	36 (1–86)	<0.001
Race				0.69				0.72
Non-Hispanic white	238 (68)	33 (73.3)	205 (67.2)		25,448 (76.4)	3022 (76.7)	22,426 (76.3)	
Non-Hispanic black	90 (25.7)	10 (22.2)	80 (26.2)		5711 (17.1)	657 (16.7)	5054 (17.2)	
Other	22 (6.3)	2 (4.4)	20 (6.6)		2167 (6.5)	259 (6.6)	1908 (6.5)	
Charlson-Deyo comorbidity score				0.45				<0.001
0	299 (85.4)	41 (91.1)	258 (84.6)		29,072 (87.2)	3540 (89.9)	25,532 (86.9)	
1	35 (10)	4 (8.9)	31 (10.2)		3593 (10.8)	348 (8.8)	3245 (11)	
2	12 (3.4)	0	12 (3.9)		537 (1.6)	39 (1)	498 (1.7)	
3	4 (1.1)	0	4 (1.3)		124 (0.4)	11 (0.3)	113 (0.4)	
AJCC clinical T stage				<0.001				<0.001
cT1	77 (22)	21 (46.7)	56 (18.4)		4455 (13.4)	812 (20.6)	3643 (12.4)	
cT2	123 (35.1)	15 (33.3)	108 (35.4)		15,829 (47.5)	1932 (49.1)	13,897 (47.3)	
cT3	61 (17.4)	2 (4.4)	59 (19.3)		7619 (22.9)	685 (17.4)	6934 (23.6)	
cT4	73 (20.9)	3 (6.7)	70 (23)		4644 (13.9)	413 (10.5)	4231 (14.4)	
cTx	16 (4.6)	4 (8.9)	12 (3.9)		779 (2.3)	96 (2.4)	683 (2.3)	
AJCC clinical N stage				<0.001				<0.001
cN0	93 (26.6)	4 (8.9)	89 (29.2)		12,054 (36.2)	1644 (41.7)	10,410 (35.4)	
cN1	155 (44.3)	20 (44.4)	135 (44.3)		15,680 (47.1)	1979 (42.6)	14,001 (47.6)	
cN2	56 (16)	19 (42.2)	37 (12.1)		3114 (9.3)	348 (8.8)	2766 (9.4)	
cN3	39 (11.1)	2 (4.4)	37 (12.1)		1769 (5.3)	183 (4.7)	1586 (5.5)	
cNx	7 (2)	0	7 (2.3)		709 (2.1)	84 (2.2)	625 (2.1)	
AJCC clinical stage[a]				0.32				<0.001
1	14 (4.2)	0	14 (4.8)		2256 (6.9)	467 (12.1)	1789 (6.2)	
2	150 (45.3)	18 (43.9)	132 (45.5)		18,056 (55.5)	2191 (56.9)	15,865 (55.3)	
3	167 (50.5)	23 (56.1)	144 (49.7)		12,238 (37.6)	1196 (31)	11,042 (38.5)	
Histology				0.20				<0.001
IDC	315 (90)	38 (84.4)	277 (90.8)		28,059 (84.2)	3540 (89.9)	24,519 (83.4)	
ILC	13 (3.7)	1 (2.2)	12 (3.9)		2101 (6.3)	142 (3.6)	11,959 (6.7)	

TABLE 1 continued

Variables	No-surgery cohort				Surgery cohort			
	All patients	Response to neoadjuvant chemotherapy		*P* Value	All patients	Response to neoadjuvant chemotherapy		*P* Value
		Clinical CR	Non-clinical CR			Pathologic CR	Non-pathologic CR	
	N = 350 (100%) *n* (%)	*N* = 45 (12.9%) *n* (%)	*N* = 305 (87.1%) *n* (%)		*N* = 33,326 (100%) *n* (%)	*N* = 3938 (11.8%) *n* (%)	*N* = 29,388 (88.2%) *n* (%)	
IDC + ILC	13 (3.7)	4 (8.9)	9 (3)		1275 (3.8)	93 (2.4)	1182 (4)	
Other	9 (2.6)	2 (4.4)	7 (2.3)		1891 (5.7)	163 (4.1)	1728 (5.9)	
MBR grade[a]				0.50				<0.001
1	9 (4.5)	0	9 (4.9)		2831 (9.7)	239 (7.5)	2592 (10)	
2	63 (31.3)	5 (26.3)	58 (31.9)		11,653 (40.2)	1033 (32.4)	10,620 (41.1)	
3	129 (64.2)	14 (73.7)	115 (63.2)		14,556 (50.1)	1915 (60.1)	12,641 (48.9)	
ER status[a]				0.10				<0.001
Positive	168 (48.8)	15 (36.6)	153 (50.5)		21,527 (64.9)	2005 (51.3)	19,522 (66.7)	
Negative	176 (51.2)	26 (63.4)	150 (49.5)		11,628 (35.1)	1900 (48.7)	9728 (33.3)	
PR status[a]				0.23				<0.001
Positive	129 (32.5)	12 (29.3)	117 (38.6)		18,004 (55.4)	1603 (41.2)	16,401 (56.2)	
Negative	215 (62.5)	29 (70.7)	186 (61.4)		15,095 (45.6)	2289 (58.8)	12,806 (43.8)	
HER2 status[a]				0.46				<0.001
Positive	96 (29.3)	14 (35)	82 (28.5)		8327 (26.1)	1369 (36.8)	6958 (24.7)	
Negative	232 (70.7)	26 (65)	206 (71.5)		23,622 (73.9)	2355 (63.2)	21,267 (75.3)	
Receptor status[a]				0.53				<0.001
HR +/HER2–	123 (37.5)	12 (30)	111 (38.5)		15,450 (48.4)	1156 (31,1)	14,294 (50.7)	
HR +/HER2+	45 (13.7)	5 (12.5)	40 (13.9)		5796 (18.2)	819 (22)	4977 (17.6)	
HR–/HER2+	51 (15.5)	9 (22.5)	42 (14.6)		2520 (7.9)	547 (14.7)	1973 (7)	
HR–/HER2–	109 (33.2)	14 (35)	95 (33)		8164 (25.6)	1199 (32.2)	6965 (24.7)	
Radiation therapy[a]				<0.001				<0.001
Yes	106 (30.8)	33 (73.3)	73 (24.4)		26.019 (78.3)	2914 (74.1)	23,105 (78.9)	
No	238 (69.2)	12 (26.7)	226 (75.6)		7211 (21.7)	1016 (25.9)	6195 (21.1)	
Adjuvant endocrine therapy[a]				0.07				<0.001
Yes	62 (19.5)	12 (29.3)	50 (18.1)		22,126 (67.7)	2165 (56.1)	19,961 (69.3)	
No	256 (80.5)	29 (70.7)	227 (81.9)		10,548 (32.3)	1695 (43.9)	8853 (30.7)	

National Cancer Data Base (NCDB) 2010–2015

CR Complete response; *AJCC* American joint committee on cancer; *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma; *MBR* modified Bloom-Richardson; *ER* estrogen receptor; *PR* progesterone receptor; *HER2* human epidermal growth factor receptor 2; *HR* hormone receptor

[a]Missing data not included and percentages calculated for available data

In the nonsurgical group, 19.5% (n = 62) of the patients received adjuvant endocrine therapy (29.3% of cCR vs 18.1% of no-cCR; p = 0.07), and 30.8% (n = 106) received radiation therapy (73.3% of cCR vs 24.4% of no-cCR; $p < 0.001$). In the multivariable analysis, the significant predictors for cCR after NCT were clinical stage T2 or lower (odds ratio [OR], 6.56; 95% confidence interval [CI], 2.48–17.32; $p < 0.001$) and nodal positivity (OR, 5.02; 95% CI, 1.71–14.69; p = 0.003).

During a median follow-up time of 30 months, Kaplan–Meier survival analysis showed significant 5-year OS differences between the groups (96.8% for cCR, 86.2% for cPR, 63.2% for cR, and 58.9% for NR; p = 0.012, log rank) (Fig. 2). The 5-year OS was 96.8% for the cCR group and 69.8% for the no-cCR group (p = 0.004) (Fig. 2).

The differences in OS between the surgical and nonsurgical cohorts were compared (Figs. 3 and 4). The 5-year OS was 79% for the surgical cohort and 74.8% for the nonsurgical cohort (p = 0.003). To validate the OS difference between the pCR and no-pCR after NCT for the surgical cohort, we performed a Kaplan–Meier survival analysis, which showed a significant OS difference in favor of the pathologic complete responders (87.3% for pCR vs 77.8% for no-pCR; $p < 0.001$) (Fig. 3). Additionally, for the patients in the surgical cohort who achieved pCR versus the patients in the nonsurgical cohort who achieved cCR (complete responders), the 5-year OS rates were respectively 92.5% (median follow-up period, 43 months) and 96.8% (median follow-up period, 37 months) (p = 0.15) (Fig. 4).

Finally, the survival analysis comparing the complete responder patients without surgery who received radiotherapy and the complete responder patients with breast-conservation surgery (BCS) who received radiotherapy demonstrated no significant OS difference (86.9% for BCS + radiotherapy vs 95.7% for no surgery + radiotherapy; p = 0.26) (Fig. 4).

DISCUSSION

Findings have shown long-term survival to be similar between NCT and adjuvant chemotherapy.[11,12] Additionally, patients who achieve pCR have better survival than patients who do not achieve pCR. The United States Food and Drug Administration and the European Medicine Agency are considering pCR as an end point for accelerated approval for the development of new treatments and drugs for high-risk operable breast cancers.[13,14]

The current practice for patients who received NCT for non-metastatic breast cancer is surgery to the breast and axilla regardless of response. Omitting cancer surgery for clinical complete responders is not a new concept, but until recently, it had largely been abandoned. No surgery for clinical complete responders after neoadjuvant treatment has been accepted for different fields and specific

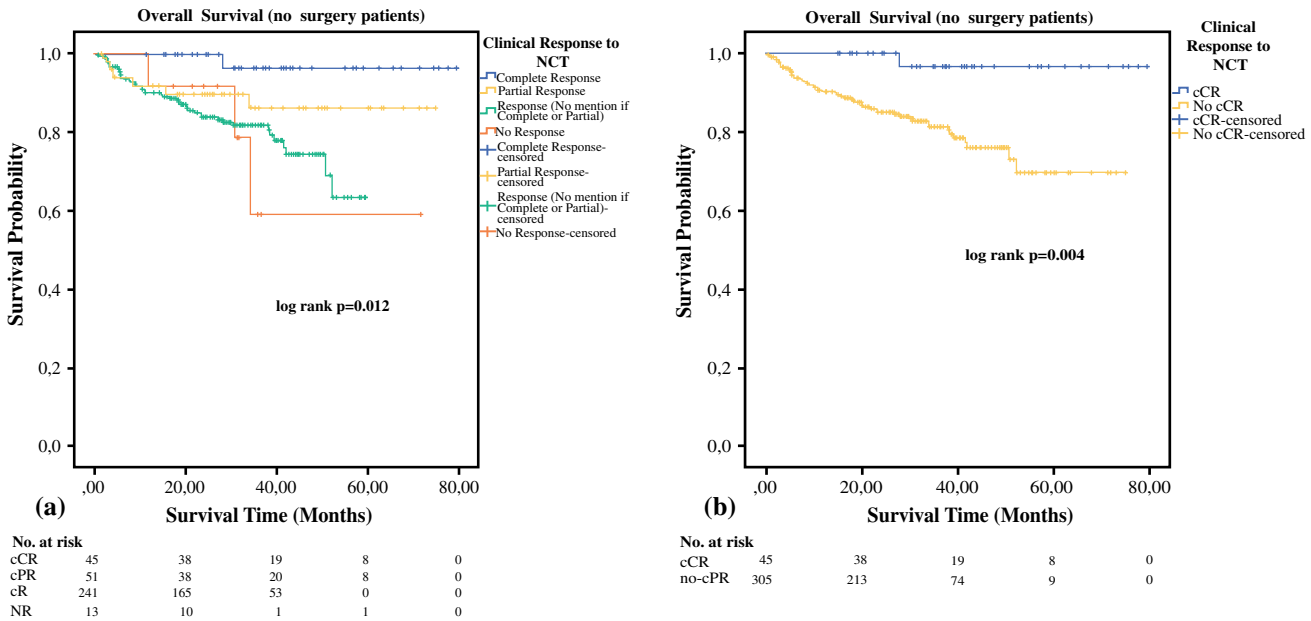

FIG. 2 Kaplan–Meier survival plots for patients without surgery after neoadjuvant chemotherapy (**a**) for all subtypes of clinical response and (**b**) for clinical response grouped as complete versus no complete response. NCT, neoadjuvant chemotherapy; cCR, clinical complete response; cPR, clinical partial response; cR, clinical response (not recorded if complete or partial); NR, no response

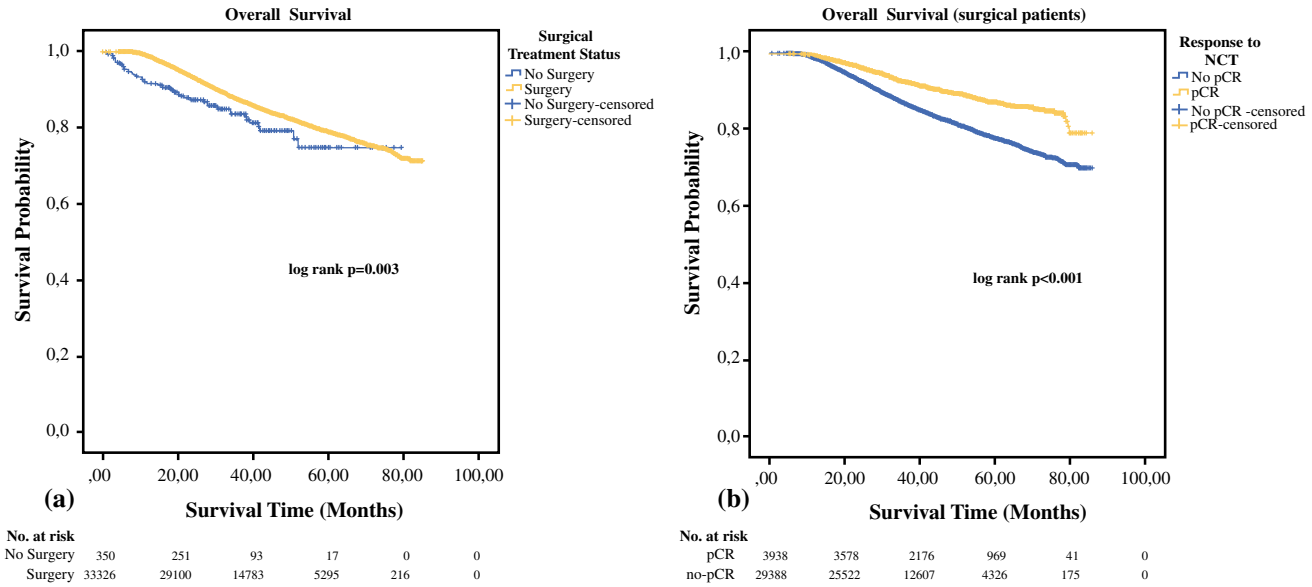

FIG. 3 Kaplan-Meier survival plots for neoadjuvant chemotherapy patients in the National Cancer Data Base (NCDB). Survival analysis was performed (**a**) if surgical treatment was received or not and (**b**) if surgical patients had a pathologic response to neoadjuvant chemotherapy (NCT). pCR, pathologic complete response

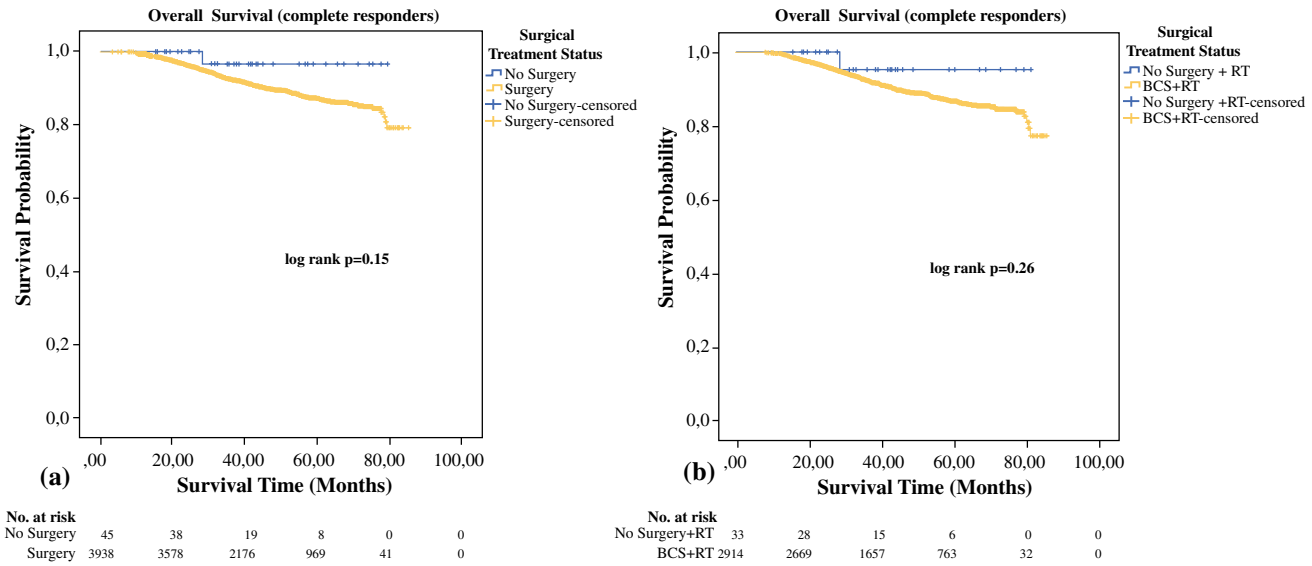

FIG. 4 Kaplan-Meier survival plots for neoadjuvant chemotherapy patients who showed a complete clinical response without surgery and a complete pathologic response with surgery in the National Cancer Data Base (NCDB). Survival analysis was performed (**a**) for complete responders and (**b**) for radiation therapy effect on clinical complete response cases without surgery and pathologic complete response cases with breast-conserving surgery. RT, radiotherapy; BCS, breast-conservation surgery

subgroups in surgical oncology such as gastrointestinal tract cancers (esophageal, gastric, and anal cancers) and prostate cancer.[15]

Breast surgical oncology saw its first attempts to omit surgery in the late 1970s.[16] However, these trials showed unacceptable rates of LRR, and omission of surgery was abandoned. This abandonment was due to a lack of effective therapies with low cCR and pCR rates, imprecise radiotherapy, and lack of precise imaging methods to determine cCR patients concordant with pCR.

Identifying cCR patients before surgery is easier than in the past, but still needs to be improved. The possibility of omitting surgery for some patients after NCT is emerging as a new research field.[17] However, none of the imaging

methods, not even trimodality imaging (mammography, ultrasound, magnetic resonance imaging), gives adequate information for choosing cCR patients concordant with pCR whose surgery can be omitted.[18–20]

Different international research groups have completed feasibility trials and ongoing clinical trials that investigate omitting surgery for exceptional responders after NCT.[9,17,21–24] These trials have focused on accurate prediction of the residual disease in the setting of NCT with the help of image-guided biopsy. Despite some differences between inclusion criteria, clinical evaluation, and biopsy techniques, principally in these trials, non-metastatic operable patients underwent clinical evaluation and image-guided biopsy after completion of NCT and before definitive surgery. The biopsy results and final pathology results were compared for sensitivity, specificity, predictivity, and accuracy of the pre-surgical biopsy.[25] These trials demonstrated that multiple biopsies with adequate technique can clinically predict pCR after completion of NCT.

Currently, an ongoing phase 2 study conducted by MD Anderson Cancer Center is investigating omission of surgery for T1-2, N0-1, HER2 +, and TNBC patients who received NCT and achieved pCR with a minimum of 12 cores using vacuum-assisted 9-gauge core biopsies.[15] Patients who show achievement of pCR on biopsy will no longer receive surgery, but instead will be treated with whole-breast radiotherapy. The primary end point is ipsilateral breast tumor recurrence-free survival.[15]

Our study investigated a cohort of 350 patients who did not undergo surgery after NCT. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) considers that at least 36 months of follow-up evaluation are necessary for effective survival analysis.[8] The follow-up time for the nonsurgical cohort was short (30 months), but the follow-up time was 37 months for the nonsurgical cCR subgroup ($n = 45$). Because 95% of the nonsurgical cohort had Charlson-Deyo comorbidity scores of 0 (85.4%) and 1 (10%), the comorbidity score was not higher than 1 for the entire nonsurgical cCR sub-group (Table 1). Therefore, we can make an inference that OS may represent survival depending on primary breast cancer.

In the literature, response rates depend on tumor characteristics, specifically tumor subtypes. Patients with HER2 + and TNBC tend to achieve a higher pCR, reaching 60–80%.[11] Similarly, the cCR rates for the nonsurgical cohort in the NCDB records are the highest for the patients with HER2 + and TNBC subtypes (28.7% and 12.8%, respectively) and lowest for the patients with an HR + subtype (9.8%), yet not as high as mentioned in the literature for the HER2 + and TNBC subtypes.

In the current study, another factor affecting the cCR rate was clinical T stage, with T1 and T2 showing higher rates of response. This also was stated in a pooled analysis by the CTNeoBC group[8] and in a meta-analysis by Li et al.[12]

Another area of discordance in our study was the use of radiotherapy after completion of NCT. Previous and ongoing trials necessitated a radiotherapy alternative to surgery when surgery was omitted.[25] In our nonsurgical cohort, significantly more patients in the cCR subgroup received radiotherapy than in the non-cCR group (73.3% vs 24.4%; $p < 0.001$; Table 1), and this could have affected OS rates.

Our study had several other limitations and challenges. First, as mentioned earlier, the NCDB records report OS only for each case and does not report disease-free survival, LRR-free survival, or other types of survival. We tried to overcome this by analyzing the Charlson-Deyo comorbidity score of the patients.

Second, although NCDB neoadjuvant data are available between 2010 and 2015, we had a short follow-up time for the nonsurgical cohort (median, 30 months).

Third, the clinical response to NCT is recorded from physician's notes, which can be subjective. It is unclear whether the physician determined the response by physical examination only, imaging only, or the two combined. Besides, if the patient had surgery, only pathologic response is mentioned, not the clinical response before surgery so a comparison between cCR and pCR can be made between the surgical and nonsurgical groups.

Fourth, our study had a low response rate and a lack of information on the clinical response rate, which is more important because we had a large number of patients for whom the type of clinical response they achieved with NCT was unknown to us. Additionally, the NCDB has no information about names of agents (chemotherapy, anti-HER2 therapy) used in treatment regimens.

Finally, due to the small sample size of cases with cCR ($n = 45$) and only one event that occurred, the statistical analysis was not strong.

To the best of our knowledge, this is the largest retrospective cohort study to analyze nonsurgical patients after NCT. This retrospective cohort study demonstrated that active surveillance or de-escalating therapy to the primary tumor site could be a possible option to consider for patients who achieve cCR after NCT as part of a clinic trial. The results from ongoing trials together with new drug combination therapies and improved imaging and biopsy techniques may help physicians to identify patients who may not need surgery to the breast after NCT.

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