The Oncologist, 2025, **30**, oyae346
https://doi.org/10.1093/oncolo/oyae346
Advance access publication 5 March 2025
Original Article

Benefit of adjuvant chemotherapy for T1cN0M0 and selected T1bN0M0 triple-negative breast cancer: a nationwide cancer registry-based study

Chiao Lo[1,2], Dwan-Ying Chang[3,4], Yen-Shen Lu[3,4], Ming-Yang Wang[1,5], Li-Wei Tsai[2,5], Chiun-Sheng Huang[1,6], Chao-Hsiun Tang[*,7], Ching-Hung Lin[*,3,4]

[1]Department of Surgery, National Taiwan University Hospital, Taipei 100225, Taiwan,
[2]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei 100229, Taiwan,
[3]Department of Oncology, National Taiwan University Hospital, Taipei 100225, Taiwan,
[4]Department of Medical Oncology, National Taiwan University Hospital, Cancer Center Branch, Taipei 106037, Taiwan,
[5]Department of Surgical Oncology, National Taiwan University Hospital, Cancer Center Branch, Taipei 106037, Taiwan,
[6]Department of Surgery, College of Medicine, National Taiwan University, Taipei 100233, Taiwan,
[7]School of Health Care Administration, College of Management, Taipei Medical University, Taipei 235603, Taiwan

[*]Corresponding authors: Ching-Hung Lin, MD, PhD, National Taiwan University Hospital, Cancer Center Branch. No.57, Ln. 155, Sec. 3, Keelung Rd., Da'an Dist., Taipei City 106, Taiwan. E-mail: chinghlin@ntu.edu.tw; Chao-Hsiun Tang, PhD, School of Health Care Administration, College of Management, Taipei Medical University, 11F, Biomedical Technology Building No. 301 Yuantong Road, Zhonghe District, New Taipei City 235, Taiwan. E-mail: chtang@tmu.edu.tw

Abstract

Background: The efficacy of adjuvant chemotherapy for T1N0M0 triple-negative breast cancer (TNBC) has not been clearly elucidated. Thus, we aimed to evaluate the efficacy of adjuvant chemotherapy for patients with T1a–cN0M0 TNBC.

Patients and methods: Patients newly diagnosed with TNBC between 2011 and 2015 were identified and followed up until the end of 2020 using the Taiwan Cancer Registry. Univariate and multivariate Cox proportional hazards regression analyses were performed to compare the recurrence-free survival (RFS) and OS between patients who received and those who did not receive adjuvant chemotherapy.

Results: Of the 62 483 patients registered during 2011-2015, 1074 patients with T1N0M0 TNBC (T1a, $n = 103$; T1b, $n = 167$; and T1c, $n = 804$) who underwent definitive breast surgery were included. Overall, 850 (79%) patients received adjuvant chemotherapy; these comprised 24.3%, 67.7%, and 88.6% of the patients with T1a, T1b, and T1c disease, respectively. Over a median follow-up of 7.18 years, a significant RFS and OS benefit from adjuvant chemotherapy was observed in the T1c subgroup but not in the T1a and T1b subgroups. However, subgroup analysis of T1b disease indicated that adjuvant chemotherapy yielded an OS benefit to patients with histological grade III disease (adjusted hazard ratio = 0.08, 95% CI, 0.01-0.77; $P = .03$).

Conclusions: Adjuvant chemotherapy improved the RFS and OS in patients with T1cN0M0 TNBC and improved the OS in patients with histological grade III T1bN0M0 disease. Our study advocates for the utilization of adjuvant chemotherapy in patients diagnosed with T1cN0M0 and histological grade III T1bN0M0 TNBC.

Key words: triple-negative breast neoplasms; chemotherapy; adjuvant; registries; Taiwan.

Implications for practice

Our study supports adjuvant chemotherapy for T1cN0 and T1b grade III TNBC.

Introduction

Breast cancer is the most common cancer worldwide.[1] It is a heterogeneous disease comprising different subtypes,[2] each with distinct clinical outcomes and therapeutic responses.[3] Triple-negative breast cancer (TNBC) accounts for approximately 10%-20% of all cases of breast cancer.[4] It is characterized by deficient estrogen receptor (ER) and progesterone receptor (PR) expression and an absent human epidermal growth factor receptor 2 (Her2) overexpression or amplification. Due to the lack of hormone receptor (HR) and Her2 overexpression or amplification, chemotherapy is the major systemic treatment strategy for early TNBC. Patients with T1a (1-5 mm), T1b (5-10 mm), and T1c (10-20 mm) node-negative early breast cancer have a favorable prognosis.[5,6] However, TNBC is associated with poor survival even in patients with stage I breast cancer.[7,8] In fact, the survival of patients with TNBC is the poorest among those of patients with other breast cancer subtypes.[5,9,10] Several phase III clinical trials on adjuvant chemotherapy for early breast cancer have excluded patients with stage I breast cancer.[11,12] Although some trials have included

Received: 16 March 2024; Accepted: 13 November 2024.
© The Author(s) 2025. Published by Oxford University Press.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

patients with T1cN0[13-17] and T1bN0[18] TNBC, the proportion of the included patients is relatively small. No randomized clinical trial has been conducted to compare outcomes between patients with and without adjuvant chemotherapy specifically designed for T1N0M0 TNBC. Alternatively, some large retrospective studies have consistently revealed the benefits of adjuvant chemotherapy for T1cN0M0 TNBC; however, the results for T1a/bN0M0 TNBC remain conflicting.[19-23] A meta-analysis revealed that adjuvant chemotherapy significantly reduced the recurrence rate in patients with T1b disease but not in those with T1a disease.[19] The National Comprehensive Cancer Network guidelines for breast cancer (version 5. 2023) have recommended adjuvant chemotherapy for patients with T1cN0 or higher stage TNBC. The guidelines do not suggest adjuvant chemotherapy for patients with T1aN0 TNBC, but state that it may be considered in select patients with high-risk features (eg, a younger age and higher histological grade). The guidelines state that chemotherapy may be considered for patients with T1bN0 TNBC; however, they have not addressed the use of prognostic variables to guide chemotherapy decisions for patients with T1b tumors.[24] Because the efficacy of adjuvant chemotherapy for T1a–cN0M0 TNBC has not been clearly studied in clinical trials, we planned to use a nationwide database to evaluate the efficacy of adjuvant chemotherapy in patients with T1a–cN0M0 TNBC.

Patients and methods

Sources of data

Data on the clinicopathological characteristics, relapse, and survival of Taiwanese patients newly diagnosed with breast cancer between 2011 and 2015 and followed until the end of 2020 were collected from the Taiwan Cancer Registry (TCR) and National Death Registry. The TCR is maintained by the Health and Welfare Data Science Center (HWDC). Established in 1979, the TCR is a population-based cancer registry; it covers more than 90% of all cancer cases diagnosed annually in Taiwan and encompasses ≥50-bed capacity hospitals that offer cancer care. Its purpose is to capture and document highly detailed information on the diagnosis, treatment, and outcomes of all newly diagnosed and confirmed cases of malignancies reported to the registry. Personal information was encrypted to protect patient privacy and the assurance of confidentiality complied with the data regulations of the HWDC. The study was granted an exemption from review by the Research Ethics Committee of the National Taiwan University Hospital (no.: 202305060W).

Selection of the study participants

We identified 62 483 patients with breast cancer from the TCR using diagnostic codes C50.x from the International Classification of Disease, Tenth Revision. Among these, 44 374 patients remained after excluding those with unknown age, age <20 years or >80 years, history of malignancy before breast cancer diagnosis, no surgery for breast cancer or unknown surgical information, or unknown ER/PR/Her2 status. TNBC is defined by the following findings: (1) <1% cells staining positive for ER and PR in immunohistochemical (IHC) staining and (2) testing negative for Her2 in fluorescence in situ hybridization (FISH) or Her2 IHC scores of 0 or 1+. Therefore, individuals with IHC staining results indicating ER or PR positivity, those with positive FISH results for Her2, and those with Her2 IHC scores of 3 + were excluded from the study. Furthermore, patients who underwent anti-hormone therapy and neoadjuvant therapy were similarly excluded from the study. Finally, we identified 1074 patients newly diagnosed with T1a–T1cN0M0 TNBC between 2011 and 2015 (according to the criteria proposed in the seventh edition of the American Joint Committee on Cancer[25] (Figure 1); these were included in the study. Based

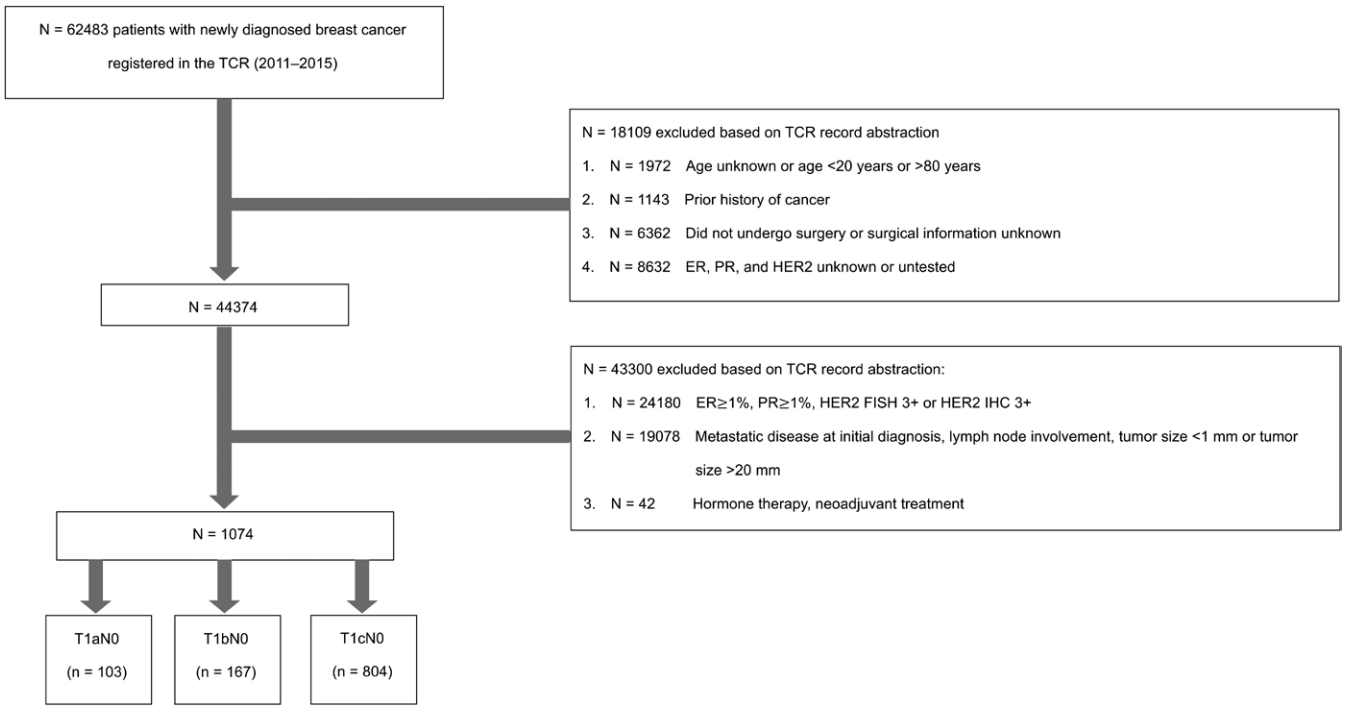

Figure 1. Flow chart of patient enrollment from the TCR. ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER 2, human epidermal growth factor receptor 2; IHC, immunohistochemical staining; PR, progesterone receptor; TCR, Taiwan Cancer Registry.

on the tumor size in the greatest dimension, these comprised 103, 167, and 804 patients with T1aN0M0 disease (size: >1 mm and ≤5 mm), T1bN0M0 disease (size: >5 mm and ≤10 mm), and T1cN0M0 disease (size: >10 mm and ≤20 mm), respectively.

Outcome measurements and variable definitions

The study endpoints were recurrence-free survival (RFS) and OS. RFS was defined as the period until any event of recurrence (including locoregional and distant disease recurrence) or all-cause death. OS was defined as the period until all-cause death. The follow-up period was the time from the date of diagnosis to the event (RFS or OS) or December 31, 2020, whichever occurred first.

Statistical analysis

Survival curves were constructed using the Kaplan-Meier method, and differences in the curves were assessed using the log-rank test. The hazard ratios (HRs) were computed with bilateral CIs. Univariate and multivariate survival analyses were performed using Cox proportional hazards models, and the HRs and corresponding 95% CIs were calculated. The multivariate Cox proportional hazards model was adjusted for age, year of diagnosis, T-stage, and histological grade. Statistical significance was defined by *P*-values of < .05. All statistical analyses were performed using SAS statistical version 9.4.

Results

Clinicopathological characteristics

Among the 1074 patients included, 921 (85.8%), 37 (3.4%), 23 (2.1%), 13 (1.2%), and 80 (7.4%) presented with invasive carcinomas of no special type, medullary carcinomas, metaplastic carcinomas, invasive lobular carcinomas, and other cancer subtypes, respectively. The demographic and clinical characteristics of these patients are listed in Table 1. The mean age was 54.4 years (SD, 10.6 years). Overall, 104 (10%), 231 (22%), 395 (37%), and 344 (32%) patients were aged 20-39, 40-49, 50-59, and 60-79 years, respectively. A total of 205 (19%), 210 (20%), 219 (20%), 210 (20%), and 230 (21%) patients were diagnosed in 2011, 2012, 2013, 2014, and 2015, respectively. Moreover, 62 (6%), 364 (34%), and 627 (58%) patients presented with histological grade I, II, and III disease, respectively. A total of 850 (79%) patients underwent adjuvant chemotherapy; these comprised 25 (24.3%), 113 (67.7%), and 712 (88.6%) patients with T1a, T1b, and T1c disease, respectively. The median follow-up for the entire study population (ie, 1074 patients) was 7.18 years; during this period, 112 cases of RFS were noted. Among these, 41 (3.8%), 33 (3.1%), and 81 (7.5%) were of locoregional recurrences, distant metastases, and all-cause deaths, respectively (Table 1).

Effect of chemotherapy on the RFS

Compared with patients with T1N0M0 TNBC who did not receive adjuvant chemotherapy, those who received adjuvant chemotherapy experienced a prolonged RFS over the median 7.18-year follow-up (crude hazard ratio [cHR] = 0.49, 95% CI, 0.33-0.72; *P* < .01]; adjusted hazard ratio [aHR] = 0.39, 95% CI, 0.25-0.62; *P* < .01; Table 2, Figure 2). A significant RFS benefit from adjuvant chemotherapy was observed in the T1c subgroup (aHR = 0.31, 95% CI, 0.19-0.52; *P* < .01), but not in the T1a (aHR = 0.71, 95% CI, 0.07-6.94; *P* = .77) and T1b (aHR = 0.58, 95% CI, 0.21-1.56; *P* = .28) subgroups (Table S1). Univariate and adjusted multivariate analyses did not indicate a significant association between age, diagnostic year, histological grade, and the RFS in patients with T1N0M0 TNBC. Adjusted multivariate analyses revealed that T1c disease was associated with a worse RFS than T1a disease (aHR = 2.34, 95% CI, 1.06-5.17; *P* = .04; Table 2).

Analysis of the T1c subgroup revealed that adjuvant chemotherapy provided an RFS benefit for both patients aged <50 years (aHR = 0.17, 95% CI, 0.06-0.44; *P* < .01) and those aged ≥50 years (aHR = 0.40, 95% CI, 0.22-0.72; *P* < .01). In patients with T1c and histological grade III disease, adjuvant chemotherapy provided an RFS benefit (aHR = 0.26, 95% CI, 0.14-0.47; *P* < .01). We examined the impact of chemotherapy on the RFS according to the age and histological grading within the T1b subgroup; however, no significant associations between chemotherapy and the RFS were found (Table 2).

Table 1. Demographic and clinicopathological characteristics of the 1074 patients with T1N0M0 TNBC included in this study.

	All patients	
Characteristics	***N***	**%**
All patients	1074	100
Age, years [mean, SD]	[54.4, 10.6]	
20-39	104	10
40-49	231	22
50-59	395	37
60-79	344	32
Year of diagnosis		
2011	205	19
2012	210	20
2013	219	20
2014	210	20
2015	230	21
T classification		
T1a	103	10
T1b	167	16
T1c	804	75
Histological grade (Nottingham)		
I	62	6
II	364	34
III	627	58
Unknown	21	2
Adjuvant chemotherapy		
No	224	21
Yes	850	79
Event		
Death	81	7.5
Locoregional recurrence	41	3.8
Distant recurrence	33	3.1

Abbreviation: TNBC, triple-negative breast cancer.

Table 2. Univariate and multivariate analyses of RFS.

	Number of patients	Number of events	%	Crude				Adjusted			
				HR	95% CI		*P*-value	HR	95% CI		*P*-value
All patients	1074	112	10.4								
Age, years											
20-39	104	8	7.7	1.00				1.00			
40-49	231	28	12.1	1.63	0.74	3.57	.22	1.73	0.79	3.82	.17
50-59	395	25	6.3	0.83	0.37	1.84	.64	0.90	0.40	2.00	.80
60-79	344	51	14.8	2.02	0.96	4.25	.07	1.97	0.93	4.19	.08
T classification											
T1a	103	8	7.8	1.00				1.00			
T1b	167	20	12.0	1.56	0.69	3.53	.29	2.24	0.97	5.19	.06
T1c	804	84	10.4	1.36	0.66	2.80	.41	2.34	1.06	5.17	.04
Year of diagnosis											
2011	205	24	11.7	1.00				1.00			
2012	210	24	11.4	1.11	0.62	1.99	.73	1.05	0.58	1.89	.87
2013	219	28	12.8	1.33	0.75	2.35	.32	1.29	0.73	2.29	.38
2014	210	16	7.6	0.82	0.42	1.57	.55	0.73	0.38	1.41	.35
2015	230	20	8.7	1.00	0.54	1.86	1.00	0.95	0.51	1.78	.88
Histological grade											
I	62	4	6.5	1.00				1.00			
II	364	39	10.7	1.68	0.60	4.70	.32	2.12	0.75	6.00	.16
III	627	67	10.7	1.66	0.60	4.55	.33	2.26	0.80	6.37	.12
Unknown	21	2	9.5	1.40	0.26	7.65	.70	1.67	0.30	9.21	.56
Adjuvant chemotherapy											
No	224	38	17.0	1.00				1.00			
Yes	850	74	8.7	0.49	0.33	0.72	<.01	0.39	0.25	0.62	<.01
T1a subgroup											
1. Age < 50 years											
No chemotherapy	10	2	20.0								
Chemotherapy	4	0	0.0								
2. Age ≥ 50 years											
No chemotherapy	68	5	7.4	1.00				1.00			
Chemotherapy	21	1	4.8	0.72	0.08	6.22	.77	1.12	0.10	13.00	.93
3. Grades I and II											
No chemotherapy	57	7	12.3	1.00				1.00			
Chemotherapy	18	1	5.6	0.49	0.06	3.97	.50	0.71	0.07	6.94	.77
4. Grade III											
No chemotherapy	17	0	0.0								
Chemotherapy	6	0	0.0								
T1b subgroup											
1. Age < 50 years											
No chemotherapy	12	2	16.7	1.00				1.00			
Chemotherapy	32	4	12.5	0.73	0.13	4.01	.72	0.15	0.02	1.42	.10
2. Age ≥ 50 years											
No chemotherapy	42	6	14.3	1.00				1.00			
Chemotherapy	81	8	9.9	0.67	0.23	1.93	.46	0.70	0.22	2.22	.54
3. Grades I and II											
No chemotherapy	32	2	6.3	1.00				1.00			
Chemotherapy	50	4	8.0	1.34	0.25	7.31	.74	2.86	0.38	21.43	.31
4. Grade III											
No chemotherapy	21	5	23.8	1.00				1.00			
Chemotherapy	62	8	12.9	0.49	0.16	1.49	.21	0.34	0.09	1.31	.12

Table 2. Continued

	Number of patients	Number of events	%	Crude				Adjusted			
				HR	95% CI		*P*-value	HR	95% CI		*P*-value
T1c subgroup											
1. Age < 50 years											
No chemotherapy	23	7	30.4	1.00				1.00			
Chemotherapy	254	21	8.3	0.21	0.09	0.50	<.01	0.17	0.06	0.44	<.01
2. Age ≥ 50 years											
No chemotherapy	69	16	23.2	1.00				1.00			
Chemotherapy	458	40	8.7	0.35	0.20	0.63	<.01	0.40	0.22	0.72	<.01
3. Grades I and II											
No chemotherapy	35	6	17.1	1.00				1.00			
Chemotherapy	234	23	9.8	0.55	0.22	1.35	.19	0.42	0.16	1.12	.08
4. Grade III											
No chemotherapy	51	16	31.4	1.00				1.00			
Chemotherapy	470	38	8.1	0.23	0.13	0.40	<.01	0.26	0.14	0.47	<.01

Abbreviations: HR, hazard ratio; RFS, recurrence-free survival.

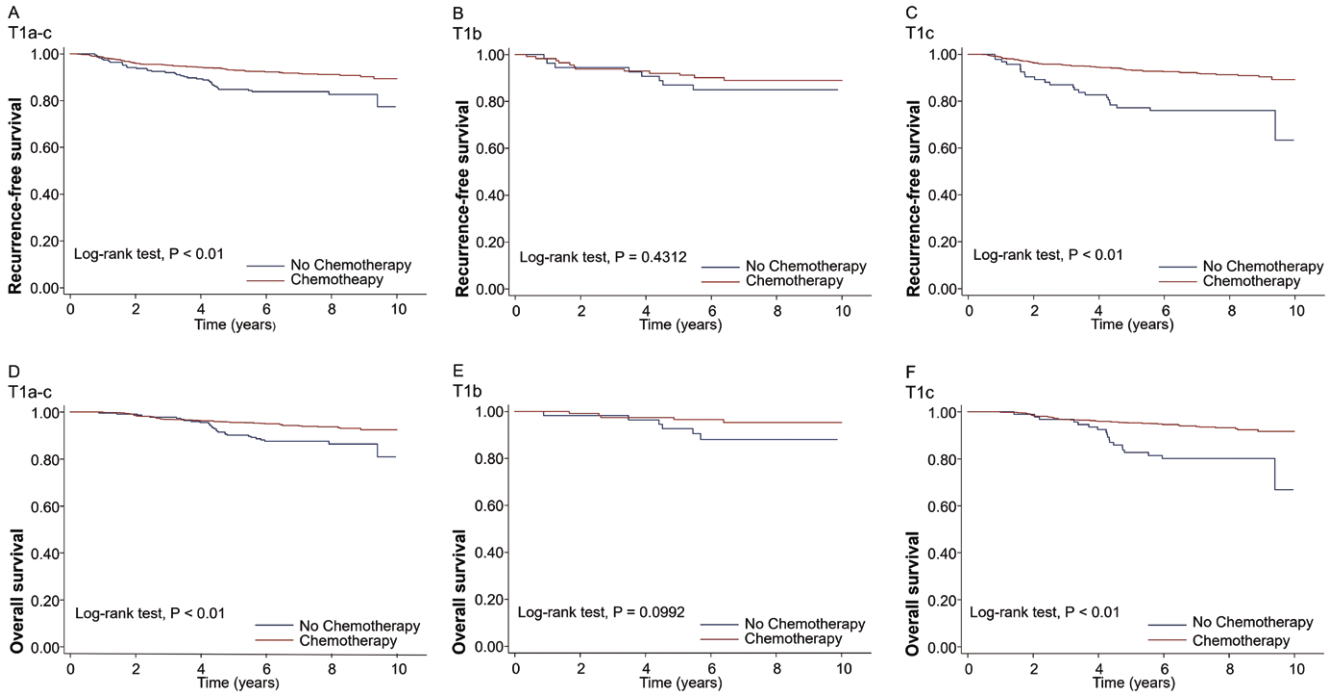

Figure 2. Kaplan-Meier curves and log-rank test findings of recurrence-free survival in patients with (A) T1a–cN0M0, (B) T1bN0M0, and (C) T1cN0M0 TNBC. Kaplan-Meier curves and log-rank test findings of overall survival in patients with (D) T1a–cN0M0, (E) T1bN0M0, and (F) T1cN0M0 TNBC. TNBC, triple-negative breast cancer.

Effect of chemotherapy on the OS

Kaplan-Meier curves revealed that compared with patients with T1N0M0 TNBC who did not receive adjuvant chemotherapy, those who received adjuvant chemotherapy exhibited an extended OS over the median 7.18-year follow-up (log-rank test, $P < .01$; Figure 2). A significant OS benefit from adjuvant chemotherapy (Figure 2) was observed in the T1c subgroup (aHR = 0.30, 95% CI, 0.17-0.53; $P < .01$) but not in the T1b subgroup (aHR = 0.35, 95% CI, 0.09-1.31; $P = .12$) (Table S2).

Both univariate and adjusted multivariate analyses demonstrated an OS benefit in patients with T1N0M0 TNBC who received adjuvant chemotherapy (cHR = 0.45, 95% CI, 0.29-0.71 [$P = .001$]; aHR = 0.31, 95% CI, 0.19-0.52 [$P < .01$]) (Table 3). Adjusted multivariate analyses revealed that T1c disease was associated with a worse OS (aHR = 4.22, 95% CI, 1.45-12.29; $P = .01$) (Table 3).

Analysis of the T1b and T1c subgroups revealed that adjuvant chemotherapy conferred an OS benefit in patients with histological grade III disease (T1b: aHR = 0.08, 95% CI,

0.01-0.77 [P = .03]; T1c: aHR = 0.23, 95% CI, 0.12-0.45 [P < .01]). Adjuvant chemotherapy also provided an OS benefit in both individuals aged <50 years (aHR = 0.19, 95% CI, 0.07-0.53; P < .01) and those aged ≥50 years (aHR = 0.39, 95% CI, 0.20-0.76; P = .01) in the T1c subgroup (Table 3).

Discussion

In this nationwide cohort study (median follow-up: 7.18 years), significant RFS and OS benefits were observed from adjuvant chemotherapy for T1c disease but not for T1a or T1b disease. This is consistent with the findings from several studies that have demonstrated survival advantages of chemotherapy in patients with T1c TNBC but not in those with T1b TNBC.[26-29] In a study on 345 patients, Ren et al reported a significant improvement in the RFS with adjuvant chemotherapy in patients with T1c disease (HR = 0.24, 95% CI, 0.08-0.76; P = .014) but not in those with T1b disease (HR = 0.32, 95% CI, 0.03-3.18; P = .33). Univariate analysis of patients with T1b disease did not reveal any factors associated with an RFS benefit from chemotherapy.[26] Zhang et al performed a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) database for the period from 2010 to 2015; they reported a significant improvement in the survival probability (HR = 3.103, 95% CI, 2.380-4.046; P < .001) and breast cancer-specific survival probability (BCSS; HR = 1.781, 95% CI, 1.243-2.551; P = .002) when patients with T1c disease received chemotherapy. However, patients with T1a TNBC and those with T1b TNBC did not experience an improved OS or BCSS with chemotherapy.[27] Walter Carbajal-Ochoa et al[28] also conducted a study using the SEER database for data recorded between 2010 and 2020; they revealed that adjuvant chemotherapy improved the OS (HR = 0.54, 95% CI, 0.47-0.62; P < .001) and BCSS (HR = 0.79, 95% CI, 0.63-0.99; P = .043) in patients with T1c TNBC. In patients with T1b disease, adjuvant chemotherapy improved the OS (HR = 0.52, 95% CI, 0.41-0.68; P < .001) but not the BCSS (HR = 0.70, 95% CI, 0.45-1.07; P = .10). No significant associations were identified between chemotherapy and the BCSS in any subgroup of T1b disease.[28]

Previous studies have yielded inconsistent results on the benefits of chemotherapy for T1b TNBC.[19,27,28] Some authors emphasize the necessity of chemotherapy for improving the survival of patients with T1b TNBC.[19,30] An et al reported a meta-analysis that revealed a significant benefit of adjuvant chemotherapy in reducing the risk of distant recurrence among patients with T1b TNBC (risk ratio = 0.62, 95% CI, 0.42-0.92; P < .05).[19] Leon-Ferre et al reported that the 5-year invasive disease-free survival of patients with T1b TNBC who did not receive systemic treatment was 67.5% (95% CI, 51.9-87.8), as compared with the 77.8% (95% CI, 68.3-83.6) of the patients with T1N0 TNBC who received systemic treatment.[30]

In our study, no significant RFS and OS benefits were observed from adjuvant chemotherapy for T1b disease. However, subgroup analysis of T1b disease indicated that adjuvant chemotherapy conferred OS benefits to patients with histological grade III disease (aHR = 0.08, 95% CI, 0.01-0.77; P = .03). In a previous study, tumor grade was identified as an independent prognostic factor for T1N0 breast cancer.[6] Our study further indicated that adjuvant chemotherapy may confer a survival benefit to patients with T1b, histological grade III TNBC. Although a large case series indicated that the histological grade was not a prognostic marker for TNBC,[31] a study on 4366 patients with T1N0M0 TNBC (based on the Netherlands Cancer Registry database) revealed histological grade III as an independent predictor for benefits from adjuvant chemotherapy[23]; this finding is consistent with the findings of our study.

Our study includes patients diagnosed over 5 years (2011-2015) and followed up until 2020. The treatment protocol for early-stage TNBC did not change significantly during the study period. The 2011 NCCN guidelines recommended no adjuvant chemotherapy for T1aN0, suggested considering adjuvant chemotherapy for T1bN0, and recommended adjuvant chemotherapy for T1cN0 TNBC. These guidelines remained unchanged from 2011 to 2015, and the latest guideline in 2024[32] provides the same recommendations. The guideline to "consider adjuvant chemotherapy" for T1bN0 TNBC highlights the lack of clinical trial evidence to guide treatment. In our study, 54 (32%) patients with T1bN0 TNBC did not receive adjuvant chemotherapy, whereas 113 (68%) did.

Variations in diagnostic techniques and supportive care during this period could influence outcomes. However, since neoadjuvant chemotherapy had not yet become the standard treatment for stage I TNBC, surgery could provide accurate pathological staging, suggesting that diagnostic techniques may not have impacted the results. Regarding supportive care, advancements in anti-emetics and the use of granulocyte colony-stimulating factor may have reduced side effects and increased chemotherapy dose intensity. Nevertheless, most of these medications were approved before 2011.

In our study, adjuvant chemotherapy improved RFS and OS in T1cN0 patients and enhanced OS in histological grade III T1bN0 patients. Our findings align with the results from a SEER database study conducted by Carbajal-Ochoa et al,[28] except for the grade II and grade I T1bN0 subgroups. Ethnicity is a significant factor in cancer research. Using data from the TCR, our study primarily focuses on an Asian population, whereas the study by Carbajal-Ochoa et al[28] included a more diverse population, comprising non-Hispanic White, non-Hispanic Black, Hispanic, and other groups such as non-Hispanic Asian/Pacific Islanders and non-Hispanic American Indian/Alaska Natives. Notably, non-Hispanic Asian/Pacific Islanders and non-Hispanic American Indian/Alaska Natives comprised only 8% of their study population. Our study, therefore, offers more detailed insights into this issue within an Asian population. A recent study analyzing the US National Cancer Database (2010-2019) showed racial and ethnic disparities in pathologic complete response and OS among TNBC patients treated with neoadjuvant chemotherapy. While the pathologic complete response rate among patients of Asian ancestry was not significantly different from that of other races, Asian ancestry was significantly associated with favorable overall survival (HR, 0.64 [95% CI, 0.55-0.75], P < .001) after adjusting for patient and disease factors as well as the pathologic complete response rate.[33] Future studies involving diverse populations are required to validate our results.

Our study had some limitations. We acknowledge that the retrospective design is a limitation of this study. Furthermore, factors not recorded in the TCR may reduce the power of the analysis. For example, detailed chemotherapy regimens are not available in the TCR. Nevertheless, as breast cancer patients in Taiwan are rarely treated in clinics, when the

Table 3 Univariate and multivariate analyses of OS.

	Number of patients	Number of events	%	Crude				Adjusted			
				HR	95% CI		*P*-value	HR	95% CI		*P*-value
All patients	1074	81	7.5								
Age, years											
20-39	104	4	3.8	1.00				1.00			
40-49	231	24	10.4	2.85	0.99	8.21	.05	3.13	1.08	9.06	.04
50-59	395	15	3.8	1.02	0.34	3.06	.98	1.15	0.38	3.48	.81
60-79	344	38	11.0	3.08	1.10	8.62	.03	3.04	1.08	8.59	.04
T classification											
T1a	103	4	3.9	1.00				1.00			
T1b	167	11	6.6	1.69	0.54	5.29	.37	2.61	0.82	8.32	.11
T1c	804	66	8.2	2.15	0.78	5.89	.14	4.22	1.45	12.29	.01
Year of diagnosis											
2011	205	19	9.3	1.00				1.00			
2012	210	20	9.5	1.17	0.61	2.23	.63	1.11	0.58	2.12	.76
2013	219	19	8.7	1.18	0.61	2.29	.62	1.13	0.58	2.20	.72
2014	210	10	4.8	0.68	0.31	1.50	.34	0.61	0.28	1.35	.22
2015	230	13	5.7	0.96	0.46	2.02	.92	0.92	0.44	1.94	.83
Histological grade											
I	62	2	3.2	1.00				1.00			
II	364	28	7.7	2.41	0.57	10.10	.23	2.78	0.66	11.76	.17
III	627	49	7.8	2.39	0.58	9.84	.23	2.87	0.68	12.12	.15
Unknown	21	2	9.5	2.72	0.38	19.29	.32	2.87	0.40	20.76	.30
Adjuvant chemotherapy											
No	224	29	12.9	1.00				1.00			
Yes	850	52	6.1	0.45	0.29	0.71	.001	0.31	0.19	0.52	<.01
T1a subgroup											
1. Age < 50 years											
No chemotherapy	10	1	10.0								
Chemotherapy	4	0	0.0								
2. Age ≥ 50 years											
No chemotherapy	68	3	4.4								
Chemotherapy	21	0	0.0								
3. Grades I and II											
No chemotherapy	57	4	7.0								
Chemotherapy	18	0	0.0								
4. Grade III											
No chemotherapy	17	0	0.0								
Chemotherapy	6	0	0.0								
T1b subgroup											
1. Age < 50 years											
No chemotherapy	12	1	8.3	1.00				1.00			
Chemotherapy	32	2	6.3	0.75	0.07	8.25	.81	0.57	0.03	11.26	.71
2. Age ≥ 50 years											
No chemotherapy	42	5	11.9	1.00				1.00			
Chemotherapy	81	3	3.7	0.30	0.07	1.24	.10	0.25	0.05	1.23	.09
3. Grades I and II											
No chemotherapy	32	1	3.1	1.00				1.00			
Chemotherapy	50	3	6.0	1.99	0.21	19.11	.55	5.30	0.38	74.39	.22
4. Grade III											
No chemotherapy	21	4	19.0	1.00				1.00			
Chemotherapy	62	2	3.2	0.16	0.03	0.86	.03	0.08	0.01	0.77	.03

Table 3. Continued

	Number of patients	Number of events	%	Crude				Adjusted			
				HR	95% CI		*P*-value	HR	95% CI		*P*-value
T1c subgroup											
1. Age < 50 years											
No chemotherapy	23	6	26.1	1.00				1.00			
Chemotherapy	254	18	7.1	0.23	0.09	0.58	<.01	0.19	0.07	0.53	<.01
2. Age ≥ 50 years											
No chemotherapy	69	13	18.8	1.00				1.00			
Chemotherapy	458	29	6.3	0.32	0.17	0.62	<.01	0.39	0.20	0.76	.01
3. Grades I and II											
No chemotherapy	35	4	11.4	1.00				1.00			
Chemotherapy	234	18	7.7	0.67	0.23	1.98	.47	0.52	0.16	1.68	.27
4. Grade III											
No chemotherapy	51	14	27.5	1.00				1.00			
Chemotherapy	470	29	6.2	0.20	0.11	0.38	<.01	0.23	0.12	0.45	<.01

Abbreviation: HR, hazard ratio.

government mandated that all hospitals treating >50 cancer patients per year report to the cancer registry, the TCR database likely enrolled most cancer patients. The National Health Insurance (NHI) coverage rate exceeded 99% during the study period, and its regulations primarily guided cancer care in Taiwan. Before September 1, 2012, the chemotherapy regimen was based on anthracyclines, whereas starting September 1, 2012, the NHI began covering taxanes for early-stage TNBC patients. Consequently, the treatment typically involved combining anthracyclines and taxanes after this date.

When considering the type of surgery and radiotherapy for T1N0M0 breast cancer patients, the choice of surgery is primarily influenced by patient preference. In contrast, the type of surgery largely determines the decision to undergo radiotherapy. Specifically, patients who received radiotherapy typically underwent breast-conserving therapy. A retrospective study conducted in the United States involving 646 T1-2, N0 TNBC patients found no significant difference in locoregional recurrence between those who received breast-conserving therapy and those who underwent mastectomy.[34] A meta-analysis assessing the impact of adjuvant radiotherapy on survival in TNBC revealed that, for T1-2, N0 TNBC, there was no OS benefit from radiotherapy when comparing breast-conserving therapy to mastectomy, with a pooled HR of 0.74 (95% CI, 0.43-1.29). Additionally, an analysis comparing OS between post-mastectomy radiotherapy and mastectomy alone in T1-2, N0 TNBC patients showed no survival benefit (pooled HR 1.10, 95% CI, 0.33-3.64).[35] As a result, we did not include the type of surgery or radiotherapy as variables in our analysis. Other residual confounding variables, such as ki67 value, lymphovascular invasion, and perineural invasion, were unavailable and could not be fully adjusted for in the multivariate regression analysis. However, the bias caused by these residual confounding factors may be more negligible in patients with stage I TNBC.

Additionally, the relatively small sample sizes in the T1a ($n = 103$) and T1b ($n = 167$) subgroups, even within this nationwide study, pose another limitation. This limited sample is also why a randomized clinical trial has not been conducted so far, as a small sample size can reduce statistical power and cause failure to detect an actual effect. Therefore, while the chemotherapy benefit might be detectable in grades I and II T1bN0 and T1aN0 TNBC with a larger sample size, the absolute benefit may not be clinically relevant.

Finally, the criteria for selecting patients for adjuvant chemotherapy may not be fully transparent in real-world data, and physician biases in deciding which patients receive adjuvant chemotherapy could influence the study outcomes. Further validation studies are highly warranted.

Conclusions

Our study results provide evidence that adjuvant chemotherapy confers RFS and OS benefits to patients with T1c TNBC as well as OS benefits to patients with T1b histological grade III disease. Our study advocates for the utilization of adjuvant chemotherapy in patients diagnosed with T1cN0M0 and histological grade III T1bN0M0 TNBC.

Acknowledgments

We would like to thank Editage (www.editage.com.tw) for English language editing.

Author contributions

Chiao Lo (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Writing—original draft, Writing—review & editing), Dwan-Ying Chang (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration), Yen-Shen Lu (Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision), Ming-Yang Wang (Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision), Li-Wei Tsai (Conceptualization, Data curation, Investigation, Methodology), Chiun-Sheng

Huang (Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation), Chao-Hsiun Tang (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—review & editing), and Ching-Hung Lin (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing—review & editing)

Funding

The authors declare no funding.

Conflict of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article were provided by Taiwan Cancer Registry and National Death Registry by permission. Data will be shared on request to the corresponding author with permission of Taiwan Cancer Registry and National Death Registry.

Disclaimers

Not applicable.

Research support

Not applicable.

Supplementary material

Supplementary material is available at *The Oncologist* online.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249. https://doi.org/10.3322/caac.21660
2. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406:747-752. https://doi.org/10.1038/35021093
3. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321:288-300. https://doi.org/10.1001/jama.2018.19323
4. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med*. 2010;363:1938-1948. https://doi.org/10.1056/NEJMra1001389
5. Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in breast cancer survival by molecular subtypes in the United States. *Cancer Epidemiol Biomarkers Prev*. 2018;27:619-626. https://doi.org/10.1158/1055-9965.EPI-17-0627
6. Houvenaeghel G, Goncalves A, Classe JM, et al. Characteristics and clinical outcome of T1 breast cancer: a multicenter retrospective cohort study. *Ann Oncol*. 2014;25:623-628. https://doi.org/10.1093/annonc/mdt532
7. Kim JE, Ahn HJ, Ahn J-H, et al. Impact of triple-negative breast cancer phenotype on prognosis in patients with stage I breast cancer. *J Breast Cancer*. 2012;15:197-202. https://doi.org/10.4048/jbc.2012.15.2.197
8. Theriault RL, Litton JK, Mittendorf EA, et al. Age and survival estimates in patients who have node-negative T1ab breast cancer by breast cancer subtype. *Clin Breast Cancer*. 2011;11:325-331. https://doi.org/10.1016/j.clbc.2011.05.002
9. Fallahpour S, Navaneelan T, De P, Borgo A. Breast cancer survival by molecular subtype: a population-based analysis of cancer registry data. *CMAJ Open*. 2017;5:E734-E739. https://doi.org/10.9778/cmajo.20170030
10. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:438-451. https://doi.org/10.3322/caac.21583
11. Ge J, Zuo W, Chen Y, Shao Z, Yu K. The advance of adjuvant treatment for triple-negative breast cancer. *Cancer Biol Med*. 2021;19:187-201. https://doi.org/10.20892/j.issn.2095-3941.2020.0752
12. Petrelli F, Bertaglia V, Parati MC, et al. Adjuvant chemotherapy for resected triple negative breast cancer patients: a network meta-analysis. *Breast*. 2023;67:8-13. https://doi.org/10.1016/j.breast.2022.12.004
13. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol*. 2006;24:5381-5387. https://doi.org/10.1200/JCO.2006.06.5391
14. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol*. 2017;35:2647-2655. https://doi.org/10.1200/JCO.2016.71.4147
15. Muss HB, Berry DA, Cirrincione CT, et al; CALGB Investigators. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med*. 2009;360:2055-2065. https://doi.org/10.1056/NEJMoa0810266
16. Li J, Yu K, Pang D, et al; CBCSG010 Study Group. Adjuvant capecitabine with docetaxel and cyclophosphamide plus epirubicin for triple-negative breast cancer (CBCSG010): an open-label, randomized, multicenter, phase III trial. *J Clin Oncol*. 2020;38:1774-1784. https://doi.org/10.1200/JCO.19.02474
17. Yu KD, Ye F-G, He M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6:1390-1396. https://doi.org/10.1001/jamaoncol.2020.2965
18. Wang X, Wang S-S, Huang H, et al; South China Breast Cancer Group (SCBCG). Effect of capecitabine maintenance therapy using lower dosage and higher frequency vs observation on disease-free survival among patients with early-stage triple-negative breast cancer who had received standard treatment: the SYSUCC-001 randomized clinical trial. *JAMA*. 2021;325:50-58. https://doi.org/10.1001/jama.2020.23370
19. An X, Lei X, Huang R, et al. Adjuvant chemotherapy for small, lymph node-negative, triple-negative breast cancer: a single-center study and a meta-analysis of the published literature. *Cancer*. 2020;126:3837-3846. https://doi.org/10.1002/cncr.32878
20. Vaz-Luis I, Ottesen RA, Hughes ME, et al. Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: a multi-institutional study. *J Clin Oncol*. 2014;32:2142-2150. https://doi.org/10.1200/jco.2013.53.1608
21. Oladeru OT, Singh AK, Ma SJ. Association of adjuvant chemotherapy with overall survival among women with small, node-negative, triple-negative breast cancer. *JAMA Netw Open*. 2020;3:e2016247. https://doi.org/10.1001/jamanetworkopen.2020.16247
22. de Nonneville A, Gonçalves A, Zemmour C, et al. Adjuvant chemotherapy in pT1ab node-negative triple-negative breast carcinomas: results of a national multi-institutional retrospective study. *Eur J Cancer*. 2017;84:34-43. https://doi.org/10.1016/j.ejca.2017.06.043
23. Steenbruggen TG, van Werkhoven E, van Ramshorst MS, et al. Adjuvant chemotherapy in small node-negative triple-negative breast cancer. *Eur J Cancer*. 2020;135:66-74. https://doi.org/10.1016/j.ejca.2020.04.033

24. Network., N. C. C. *Breast Cancer: NCCN Clinical Practice Guidelines in Oncology*. 2023. Accessed June 14, 2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
25. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17:1471-1474. https://doi.org/10.1245/s10434-010-0985-4
26. Ren YX, Hao S, Jin X, et al. Effects of adjuvant chemotherapy in T1N0M0 triple-negative breast cancer. *Breast*. 2019;43:97-104. https://doi.org/10.1016/j.breast.2018.11.011
27. Zhang J, Wang W, Wang J, et al. Survival outcome and impact of chemotherapy in T1 node-negative triple-negative breast cancer: a SEER database analysis. *J Oncol*. 2020;2020:8880727. https://doi.org/10.1155/2020/8880727
28. Carbajal-Ochoa W, Bravo-Solarte DC, Bernal AM, Anampa JD. Benefit of adjuvant chemotherapy in lymph node-negative, T1b and T1c triple-negative breast cancer. *Breast Cancer Res Treat*. 2023;203:257-269. https://doi.org/10.1007/s10549-023-07132-6
29. Fasano GA, Bayard S, Chen Y, et al. Benefit of adjuvant chemotherapy in node-negative T1a versus T1b and T1c triple-negative breast cancer. *Breast Cancer Res Treat*. 2022;192:163-173. https://doi.org/10.1007/s10549-021-06481-4
30. Leon-Ferre RA, Polley M-Y, Liu H, et al. Impact of histopathology, tumor-infiltrating lymphocytes, and adjuvant chemotherapy on prognosis of triple-negative breast cancer. *Breast Cancer Res Treat*. 2018;167:89-99. https://doi.org/10.1007/s10549-017-4499-7
31. Rakha EA, El-Sayed ME, Green AR, et al. Prognostic markers in triple-negative breast cancer. *Cancer*. 2007;109:25-32. https://doi.org/10.1002/cncr.22381
32. Network, N. C. C. *Breast Cancer (Version 4.2024)*. Accessed October 3, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
33. Woriax HE, Thomas SM, Plichta JK, et al. Racial/ethnic disparities in pathologic complete response and overall survival in patients with triple-negative breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol*. 2024;42:1635-1645. https://doi.org/10.1200/JCO.23.01199
34. Zumsteg ZS, Morrow M, Arnold B, et al. Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1-2N0 triple-negative breast cancer. *Ann Surg Oncol*. 2013;20:3469-3476. https://doi.org/10.1245/s10434-013-3011-9
35. O'Rorke MA, Murray LJ, Brand JS, Bhoo-Pathy N. The value of adjuvant radiotherapy on survival and recurrence in triple-negative breast cancer: a systematic review and meta-analysis of 5507 patients. *Cancer Treat Rev*. 2016;47:12-21. https://doi.org/10.1016/j.ctrv.2016.05.001