



## Assessing the Benefit of Adjuvant Chemotherapy in Patients with ER-Negative pT1-2N0M0 Mucinous Breast Carcinoma based on the SEER Database

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### Abstract

**Background:** Mucinous Carcinoma (MC) of the breast is often considered to have a better prognosis than Invasive Ductal Carcinoma (IDC). However, the National Comprehensive Cancer Network (NCCN) guidelines for the optimal systemic control of MC are mostly extrapolated from data pertaining to IDC. In this study, we investigated Breast Cancer-Specific Survival (BCSS) in different subtypes of patients with MC and analyzed whether patients with Estrogen Receptor (ER)- negative and pT1-2N0M0 MC should be treated with adjuvant chemotherapy.

**Methods:** Using data from the Surveillance, Epidemiology and End Results (SEER) cancer database (2000-2009), we analyzed the relative and absolute hazard ratios of the cumulative 10-year BCSS rate of 10,772 female operable breast cancer patients with MC, stratified by age, race, tumor size, ER status, histological grade, lymph node status, adjuvant chemotherapy and adjuvant radiotherapy.

**Results:** The rate of ER negativity was 2.7% in the MC patients. MC showed less aggressive behavior and had a better prognosis regardless of the patients' ER status, and this favorable outcome was maintained after 10 years. The univariate analyses and multivariate analysis consistently showed that ER positivity was an advantageous factor affecting the BCSS rate in the MC patients (HR=0.48, 95% CI: 0.34-0.67,  $p < 0.001$  and HR=0.62, 95% CI: 0.44-0.87,  $p = 0.006$ , respectively). In the patients with lymph node-negative disease, the 10-year BCSS rates were 91% and 88% in those with ER-positive and ER-negative MC, respectively. Specifically, among the patients with ER-negative pT1-2N0M0 MC, there was a significant difference in the 10-year BCSS rates between the patients who did not receive adjuvant chemotherapy and those who received adjuvant chemotherapy (92% vs. 81%, adjusted HR=3.02, 95% CI: 1.13-8.06,  $p = 0.028$ ).

**Conclusion:** MC histology type was a favorable factor affecting survival. No overwhelming evidence supports the significant benefit of adjuvant chemotherapy in patients with ER-negative and pT1-2N0M0 MC.

**Keywords:** Breast cancer; Mucinous adenocarcinoma; Estrogen receptor; Survival analysis; Chemotherapy

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Received Date: 14 Oct 2022

Accepted Date: 02 Nov 2022

Published Date: 07 Nov 2022

#### Citation:

Liu Y, Jiang H, Zhao Y, Bao L, Wu W, Hao S, et al. Assessing the Benefit of Adjuvant Chemotherapy in Patients with ER-Negative pT1-2N0M0 Mucinous Breast Carcinoma based on the SEER Database. *World J Surg Surgical Res.* 2022; 5: 1417.

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### Core Tip

Mucinous carcinoma of the breast is often considered to have a better prognosis than invasive ductal carcinoma. Here, we retrospectively investigated the BCSS rates in different subtypes of patients with MC.

### Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide and substantial heterogeneity exists among patients [1]. Mucinous Carcinoma (MC), which is also known as colloid carcinoma, is not a common type of breast cancer. MC reportedly accounts for 1% to 6% of all primary breast cancers [2-4]. MC usually occurs in postmenopausal women and has favorable clinicopathologic characteristics, including a lower incidence of nodal metastasis, higher expression of estrogen and progesterone receptors, and better differentiation [5-7].

Therefore, MC is often considered to have a better prognosis than Invasive Ductal Carcinoma

(IDC). Because of its low incidence rate, most reported series of MC have few patients and a limited follow-up period; thus, the prognostic significance of these clinicopathologic characteristics is not well established. The NCCN guidelines for the optimal systemic control of MC are mostly extrapolated from data pertaining to IDC.

In this study, we compared the Breast Cancer-Specific Survival (BCSS) and significance of available clinical and pathologic prognostic factors in patients with MC. We also retrospectively investigated the BCSS rates in different subtypes of patients with MC. Determining whether patients with ER-negative pT1-2N0M0 MC should be treated without systemic adjuvant chemotherapy was our primary interest.

## Patients and Methods

### Patient selection

To collect sufficient cases, we used the Surveillance, Epidemiology and End Results (SEER) database. We selected female patients with MC between 2000 and 2009. Patients diagnosed before 2000 were excluded because of the lack of chemotherapy and radiotherapy data; patients diagnosed after 2009 were excluded to ensure an adequate follow-up time.

We identified 10,772 patients who had pathology reports according to the following inclusion criteria: Female sex, age at diagnosis  $\geq 18$  years, surgical treatment with either mastectomy or breast-conserving surgery, American Joint Committee on Cancer (AJCC) stages I to III, pathologically confirmed MC, unilateral breast cancer, known time of diagnosis, known ER status and breast cancer as the first and only cancer diagnosis. Information regarding the following variables was obtained if available: Patient age, race, tumor size, regional Lymph Node (LN) status, histological grade, and treatment with or without adjuvant chemotherapy or adjuvant radiotherapy. The HER2 status was not analyzed in this study because this information was not available in the SEER database before 2010.

### Statistical analysis

With a median follow-up of 8.6 years and 75% of the patients followed up within 11.5 years since diagnosis, we restricted our analysis to the time frame of 10 years to guarantee the validity and reliability of our results. The vital status (alive or dead) was obtained. The cause of death was categorized as breast cancer-specific or non-breast cancer-related. The primary study outcome in this study was the BCSS rate, which was defined as the interval between diagnostic biopsy and death from breast cancer. In the BCSS analysis, patients who died from other causes were censored at the date of death. In the comparison of the different pathological factors, Student's t-test was applied to the counting data, and the chi-square test was applied in the comparisons of the frequencies and classifications. The 10-year survival rate was calculated by the life table's method, the survival curves were generated by the Kaplan-Meier method, and the BCSS rates were compared between the groups using the log-rank test. All statistically significant variables observed in the univariate analysis were included in the multivariate analysis using a Cox proportional hazard model. All two-sided p-values  $<0.05$  were considered statistically significant. The SPSS 24.0 software package (SPSS, Chicago, IL) was used for the statistical analysis.

## Results

### General information

From the SEER cancer database, we identified 10,772 patients with MC. The clinicopathologic characteristics of MC were compared

(Table 1). The median age of the patients with MC at diagnosis was 70 years. MC was more likely to occur in Caucasian patients, be smaller in size, have less nodal involvement, and be a lower grade and exhibit ER positivity. The rate of ER negativity was 97 (6.3%) in the MC patients who received adjuvant chemotherapy and 199 (2.2%) in the MC patients who did not receive adjuvant chemotherapy. To determine whether traditional prognostic factors would be useful in patients with MC, univariate and multivariate analyses of the BCSS rates were performed with patients with MC. All the following variables were available: Age, race, pT stage, pN stage, ER status, grade, and adjuvant chemotherapy and adjuvant radiotherapy. Univariate analysis showed that the survival of African American patients was worse than that of Caucasian patients (HR=1.52, 95% CI: 1.21-1.92,  $p<0.001$ ). However, multivariate analysis did not show the same results, suggesting that the prognosis of MC was not related to race (HR=1.22, 95% CI: 0.97-1.55,  $p=0.092$ ) (Table 2).

### Prognostic factors affecting BCSS in patients with MC

The effects of the traditional prognostic factors on BCSS are shown in Table 2. Both the univariate analysis and multivariate analysis showed that ER negativity was a favorable factor affecting survival. In the univariate analyses, ER positivity was an advantageous factor affecting the BCSS rate, with an HR of 0.48 (95% CI: 0.34-0.67,  $p<0.001$ ). After adjusting for other prognostic factors, the HR increased to 0.62 (95% CI: 0.44-0.87), with a significant p value of 0.006.

Univariate analyses showed that adjuvant chemotherapy was associated with an improved BCSS rate (HR=1.66, 95% CI: 1.39-1.98,  $p<0.001$ ). However, in the multivariate analysis, adjuvant chemotherapy was not significantly associated with the BCSS rate (HR=1.15, 95% CI: 0.92-1.44,  $p<0.228$ , Table 2). Multivariate analysis showed that age ( $\geq 60$  years), tumor size, LN status, ER status, tumor grade, and adjuvant radiotherapy were significantly associated with the BCSS rate (Table 2).

### Comparison of the BCSS rates in MC patients treated with or without adjuvant chemotherapy

In the stratification analysis, among the patients with ER-positive tumors, although there was a 6% difference in the 10-year BCSS rate in the MC patients treated with or without adjuvant chemotherapy (84% vs. 90%), this difference was not significant (HR=1.06, 95% CI: 0.84-1.34,  $p=0.626$ ). Adjuvant chemotherapy was significantly associated with the 10-year BCSS rate in patients with ER-negative tumors (70% vs. 90%, HR=3.73, 95% CI: 1.58-8.83,  $p=0.003$ ) (Table 3).

### Adjuvant chemotherapy in ER-negative and pT1-2N0M0 MC

Among the patients with pT1N0M0 MC, the 10-year BCSS rate was excellent. The BCSS rate decreased as the pathological tumor stage increased in the patients with ER-negative and node-negative MC and was 94% and 74% in the pT1N0M0 and pT2N0M0 patients, respectively. Adjuvant chemotherapy was not significantly associated with the 10-year BCSS rate in the patients with ER-negative pT1N0M0 and pT2N0M0 MC. A BCSS rate of 89% is not good enough to eliminate adjuvant chemotherapy in pT1-2N0M0 patients, and we investigated the effect of adjuvant chemotherapy on survival. However, as the sample size increased, the 10-year BCSS rates of the patients who either received or did not receive chemotherapy were 81% and 92%, respectively (Figure 1, 2). After adjusting for other prognostic factors, the multivariate analysis confirmed this effect

**Table 1:** Clinicopathologic characteristics of mucinous breast carcinoma patients from the SEER database.

Characteristic	Number (%) of patients		p-value
	Adjuvant chemotherapy (YES) (n=1,533)	Adjuvant chemotherapy (NO) (n=9,239)	
Median follow-up (months) (IQR)	105 (77-139)	105 (77-139)	
Age at diagnosis (Mean ± SD) (years)	53.58 ± 12.44	69.61 ± 13.22	<0.001
<b>Age at diagnosis (years)</b>			<0.001
<60	1,096 (71.5)	2,180 (23.6)	
≥ 60	437 (28.5)	7,059 (76.4)	
<b>Race</b>			<0.001
Caucasian	1,122(73.2)	7,681 (83.2)	
African American	173 (11.3)	751 (8.1)	
Other	238 (15.5)	807 (8.7)	
<b>Tumor size</b>			<0.001
pT1	674 (44.0)	7,012 (75.9)	
pT2	631 (41.1)	1,927(20.9)	
pT3	164 (10.7)	222 (2.4)	
pT4	64 (4.2)	78 (0.8)	
<b>Regional lymph nodes</b>			<0.001
pN0	980 (63.9)	8,737 (94.5)	
pN1	405 (26.4)	445 (4.8)	
pN2	105 (6.8)	43 (0.5)	
pN3	43 (2.8)	14 (0.2)	
<b>ER status</b>			<0.001
Negative	97 (6.3)	199 (2.2)	
Positive	1,436 (93.7)	9040 (97.8)	
<b>Grade</b>			<0.001
I	557 (36.3)	4,804 (52.0)	
II	568 (37.1)	2,431 (26.3)	
III-IV	173 (11.3)	293 (3.2)	
Unknown	235 (15.3)	1,711 (18.5)	
<b>Adjuvant radiotherapy</b>			<0.001
No	635 (41.4)	5,062 (54.8)	
Yes	898 (58.6)	4,177 (45.2)	

ER: Estrogen Receptor; IQR: Inter-Quartile Range (from the 25<sup>th</sup> percentile to the 75<sup>th</sup> percentile)

(HR=3.02, 95% CI: 1.13-8.06, p=0.028, Table 4).

## Discussion

The incidence of MC was 1% to 6%, as reported in other studies [3,8]. MC occurs more often in older patients, particularly postmenopausal women, than IDC [9-11]. Currently, few large samples are available for the comparison of the clinicopathological features of IDC and MC and the difference in the BCSS rates between the two types. This retrospective study we performed showed that the regional LNs were relatively infrequently involved, with 89.2% of the MC patients did not exhibit this type of involvement; this finding is generally consistent with the low incidence of axillary node involvement reported in other studies [12,13]. Our study, which used data from the SEER database, also showed that MC had more favorable pathologic characteristics than IDC, such as higher rates of ER positivity and lower histological grades. These observations are consistent with the findings described in other studies and indicate

that MC is an indolent disease [14,15]. In our multivariate analysis of MC, pT stage and nodal status were the most significant independent prognostic factors. The study by Salomone Di Saverio and other studies support our conclusion [16,17].

Chemotherapy is the main treatment for hormone receptor-negative breast cancer, and the biological behavior of breast cancer with different histologic types also differs [18,19]. For MC patients who are negative for ER, the NCCN guidelines recommend that the following treatment should be performed: If the stage is pT1aN0M0 (including micro-infiltration), adjuvant chemotherapy should not be performed; if the stage is pT1bN0M0, adjuvant chemotherapy should be considered; and if the stage is pT1cN0M0, adjuvant chemotherapy is recommended.

However, to the best of our knowledge, the systemic treatments for MC in the NCCN guidelines are mostly extrapolated from data pertaining to IDC. We aimed to investigate whether the BCSS rate

**Table 2:** Univariate and multivariate Cox proportional hazard model analyses of the BCSS rate.

Parameter	Univariate HR (95% CI)	log-rank <i>p</i> *	Multivariate HR# (95% CI)	Adjusted <i>p</i>
<b>Age (years)</b>		<0.001		<0.001
<60	1		1	
≥ 60	1.58 (1.32-1.88)		1.91 (1.58-2.32)	
<b>Race</b>		<0.001		
Caucasian	1		1	
African American	1.52 (1.21-1.92)	<0.001	1.22 (0.97-1.55)	0.092
Other	0.77 (0.58-1.03)	0.077	0.79 (0.59-1.05)	0.106
Unknown	0	0	0	0
<b>Tumor size</b>		<0.001		<0.001
pT1	1		1	
pT2	2.37 (2.00-2.81)		2.09 (1.75-2.49)	
pT3	5.37 (4.15-6.56)		3.99 (3.00-5.30)	
pT4	10.48 (7.62-14.41)		5.83 (4.08-8.32)	
<b>Regional lymph nodes</b>		<0.001		<0.001
pN0	1		1	
pN1	2.35 (1.92-2.92)		1.58 (1.25-1.98)	
pN2	4.62 (3.26-6.53)		2.23 (1.52-3.29)	
pN3	8.23 (5.21-13.02)		2.85 (1.72-4.71)	
<b>ER status</b>		<0.001		0.006
Negative	1		1	
Positive	0.48 (0.34-0.67)		0.62 (0.44-0.87)	
<b>Grade</b>		<0.001		
I	1		1	
II	1.43 (1.20-1.72)	<0.001	1.21 (1.00-1.45)	0.045
III	2.72 (2.05-3.61)	<0.001	1.95 (1.46-2.63)	<0.001
IV	1.40 (0.45-4.38)	0.023	0.77 (0.24-2.43)	0.652
Unknown	1.278 (1.03-1.58)	1.03	1.17 (0.95-1.45)	0.144
<b>Adjuvant chemotherapy</b>		<0.001		0.228
No	1		1	
Yes	1.66 (1.39-1.98)		1.15 (0.92-1.44)	
<b>Adjuvant radiotherapy</b>		<0.001		<0.001
No	1		1	
Yes	0.53 (0.46-0.63)		0.60 (0.51-0.70)	

BCSS: Breast Cancer-Specific Survival; CI: Confidence Interval; HR: Hazard Ratio

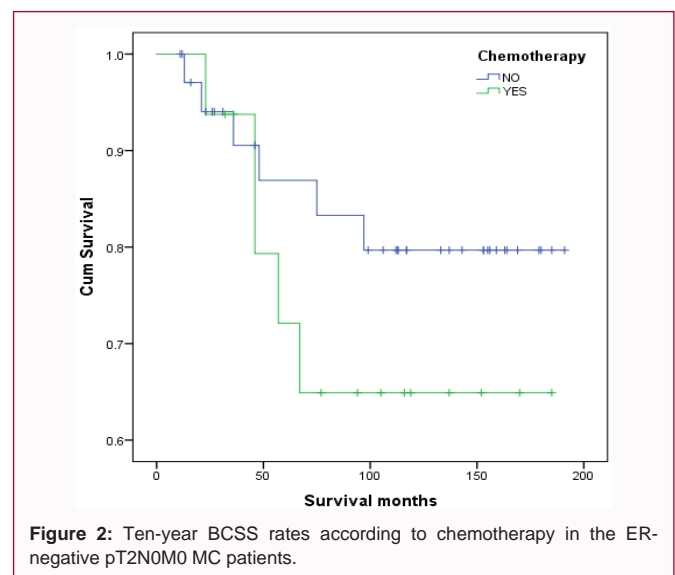
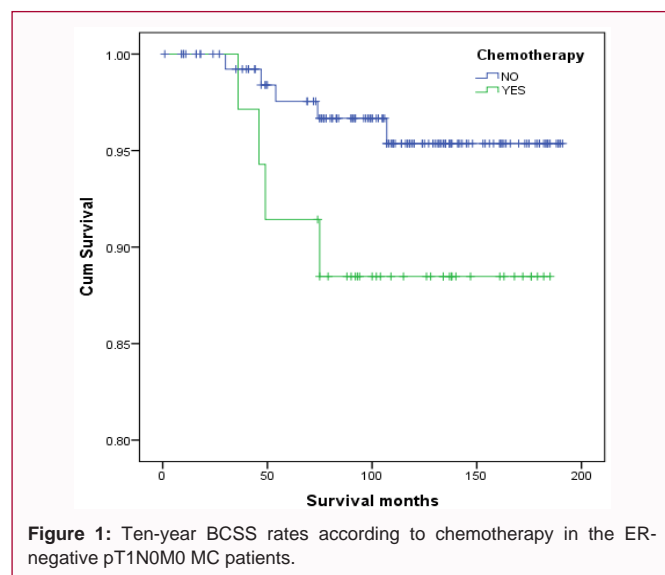
#In the SEER datasets, the HRs were adjusted for age at diagnosis, race, pT stage, regional lymph nodes, ER status, grade, adjuvant chemotherapy and adjuvant radiotherapy. A Cox regression model (method: backward, likelihood ratio) was employed to calculate the HR

**Table 3:** Ten-year BCSS rates in the MC patients treated with or without chemotherapy subgroups.

Subgroup	Number of patients	10-year BCSS (%)	Adjusted HR (95% CI)	<i>p</i> -value
<b>Overall</b>				0.228
Without Chemotherapy	9,239	90	1	
With Chemotherapy	1,533	83	1.15 (0.92-1.44)	
<b>ER positive</b>				0.626
Without Chemotherapy	9,040	90	1	
With Chemotherapy	1,436	84	1.06 (0.84-1.34)	
<b>ER negative</b>				0.003
Without Chemotherapy	31,569	90	1	
With Chemotherapy	109	70	3.73 (1.58-8.83)	

**Table 4:** Ten-year BCSS rates according to chemotherapy in the ER-negative pT1-2N0M0 MC patients.

Subgroup	Number of patients	10-year BCSS (%)	Adjusted HR (95% CI)	p-value
pT1N0M0	175	94		0.051
No chemotherapy	140	95	1	
Chemotherapy	35	88	3.93(0.99-15.59)	
pT2N0M0	52	74		0.247
No chemotherapy	36	79	1	
Chemotherapy	16	64	2.30(0.56-9.42)	
pT1-2N0M0	227	89		0.028
No chemotherapy	176	92	1	
Chemotherapy	51	81	3.02(1.13-8.06)	



of patients with ER-negative and node-negative MC differs from that of IDC patients. Although the p value was not significant due to the small sample size, we could rule out the possibility that ER-negative and node-negative MC had a better BCSS rate. Notably, ER-negative pT1N0M0 MC had a 10-year BCSS rate of 94%, which reached the “curable cancer” standard of the Worldwide Health Organization. We further confirmed that adjuvant chemotherapy did not confer a significant survival benefit in ER-negative and pT1N0M0 MC (10-year BCSS rates among patients receiving and not receiving chemotherapy were 88% and 95%, respectively). Meanwhile, although the ER-negative pT2N0M0 MC had a 10-year BCSS rate of 74%, adjuvant chemotherapy did not improve the 10-year BCSS rate. However, as the sample size increased, adjuvant chemotherapy was significantly associated with an improved 10-year BCSS rate in patients with ER-negative pT1-2N0M0 MC (HR=3.02, 95% CI: 1.13-8.06, p=0.028).

It seems that there is no overwhelming evidence supporting the significant benefit of adjuvant chemotherapy in patients with ER-negative pT1-2N0M0 MC. Therefore, adjuvant chemotherapy might be avoided in patients with ER-negative pT1-2N0M0 MC. However, this finding is inconsistent with the treatment recommended in the current NCCN guidelines [20]. Our findings raise a question regarding the reasonability of the administration of adjuvant chemotherapy in all ER-negative and pT1-2N0M0 MC, and further relevant studies are warranted.

Few clinical trials specifically focus on adjuvant chemotherapy to

treat MC. Gao et al. [21] suggested that adjuvant chemotherapy may improve prognosis in patients with negative LNs and tumors larger than 3 cm or patients with LN metastasis and tumors larger than 1 cm. However, in their study, they screened female early-stage ER/PR-positive MC patients between 1998 and 2016 from the SEER database. In our study, patients diagnosed after 2009 were excluded to ensure an adequate follow-up time. This may be the difference in ER-positive MC BCSS rates between the studies.

Our study has limitations. First, this study was based on a retrospective analysis of the SEER database rather than a prospective randomized controlled study. Second, the time span covered by the data was relatively large, and although whether chemotherapy was used was clear, the specific chemotherapy regimens were unknown. Third, the sample size was relatively small for the ER-negative and pT1-2N0M0 MC subgroup. Fourth, the HER2 status was unavailable. Moreover, no specific pathological classification of MC, such as pure mucinous carcinoma and mixed mucinous carcinoma, was defined, and different histologic types of MC may have different prognoses [19,22,23].

It is necessary to carry out a multicenter, large-sample study to investigate the effect of chemotherapy on ER-negative and pT1-2N0M0 MC.

## Conclusion

Our study suggests that the MC histology type is a favorable

factor affecting survival and that overwhelming evidence supporting the significant benefit of adjuvant chemotherapy in patients with ER-negative and pT1-2N0M0 MC is lacking. Further prospective studies are needed to confirm our findings.

## Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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