Society of Medical Education & Research

2025, Volume 5, Issue 2, Page No: 1-12

ISSN: 3108-4834

Archive of International Journal of Cancer and Allied Science

Breast Cancer-Specific Mortality in Stage IV Patients with Small Tumors: Insights from a Population-Based Cohort

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Abstract

A small primary tumor does not necessarily correspond to a favorable prognosis. We hypothesized that stage IV breast cancers with very small primary tumors accompanied by extensive lymph node metastases may reflect an aggressive tumor biology. Data spanning 2010 through 2015 were collected in a retrospective manner from the Surveillance, Epidemiology, and End Results (SEER) database. Eligible cases were limited to women with unilateral metastatic invasive ductal carcinoma classified as T1 or T2. Key variables examined in the study encompassed T stage, N stage, tumor differentiation grade, locations of metastases, count of metastatic sites, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 status. Analyses involved Kaplan-Meier survival curves and multivariable Cox regression models that included interaction terms. Rates of breast cancer-specific mortality at 1, 2, and 3 years were assessed with respect to primary tumor size. A total of 5,340 eligible breast cancer patients were included in the analysis. Multivariate analysis identified race, age, tumor grade, molecular subtype, surgical treatment, and the presence of brain or liver metastases as independent predictors of breast cancer-specific mortality (BCSM). Among T1 tumors, patients with N0, N1, or N2+ disease exhibited similar BCSM. For tumors smaller than 50 mm, reductions in tumor size did not correspond to lower 1-, 2-, or 3-year BCSM. Notably, in triple-negative breast cancers (TNBCs), the T1a/T1bN2+ subgroup demonstrated significantly higher BCSM compared with all other groups. Stage IV breast cancer patients with small primary tumors may experience breast cancer-specific mortality (BCSM) comparable to those with larger tumors. In triple-negative breast cancers (TNBCs), very small tumors accompanied by extensive lymph node involvement are linked to the poorest BCSM. Further research is warranted to better understand T1a/T1bN2+ M1 TNBCs and to guide individualized treatment strategies for these patients. This study demonstrates that in stage IV breast cancer, smaller primary tumors do not necessarily confer a survival advantage in terms of breast cancer-specific mortality (BCSM). Notably, very small triple-negative breast cancers (TNBCs) with extensive regional lymph node involvement appear to reflect an aggressive tumor biology. Given the poor prognosis associated with T1a/T1bN2+ TNBCs, there is an urgent need for more individualized treatment strategies. Future studies should investigate the genetic and molecular characteristics underlying T1a/T1bN2+ TNBCs and clarify the mechanisms driving metastatic progression from small primary tumors, which may inform the development of targeted therapies.

Keywords: Breast cancer, Stage IV patients, TNBCs, BCSM

Introduction

Approximately 6% of breast cancers are diagnosed as stage IV at initial presentation [1], representing a highly heterogeneous disease group. Despite advances in treatment, 5-year breast cancer-specific mortality (BCSM) remains disproportionately high in these patients, with 70%–80% succumbing to cancer-related causes, compared with significantly lower rates in nonmetastatic breast cancer [2]. Interestingly, around 10% of women with de novo metastatic breast cancer survive for a decade or longer, highlighting the wide variability in outcomes [3]. In metastatic disease, prognosis is influenced not only by tumor burden and metastatic distribution but also by individual patient

Access this article online https://smerpub.com/

Received: 10 March 2025; **Accepted:** 05 July 2025

How to cite this article: Schneider TL, Krüger BE. Breast Cancer-Specific Mortality in Stage IV Patients with Small Tumors: Insights from a Population-Based Cohort. Arch Int J Cancer Allied Sci. 2025;5(2):1-12. https://doi.org/10.51847/b9vFcweAVg

factors and underlying tumor biology [4–6]. Among the key determinants of prognosis—tumor size, regional lymph node (LN) status, and distant metastasis—tumor size has received comparatively little attention in stage IV disease, despite its established role in cancer progression [7]. Traditional models suggest that as tumors enlarge, they acquire enhanced potential to invade lymph nodes and distant organs [8, 9], and within any nodal category, larger tumors generally indicate worse outcomes [10]. As a result, small primary tumors with nodal involvement may be mistakenly considered low-risk, whereas they may in fact reflect aggressive biology. The concept of "self-seeding" proposes that metastatic cells can re-infiltrate the primary tumor, contributing to its growth and progression [11]. Tumor dissemination may occur long before clinical detection, indicating that tumor size alone does not necessarily reflect the timeline or aggressiveness of metastasis [12]. Indeed, very small tumors with extensive LN involvement may serve as markers of particularly aggressive disease [13], whereas large tumors that fail to spread regionally (e.g., T3N0) may demonstrate indolent biological behavior [14]. This highlights that the prognostic impact of tumor size in stage IV breast cancer is not straightforward, and small tumors may represent a distinct biological subset. Although tumor size–nodal interactions have been investigated in nonmetastatic breast cancer [13, 14], their significance in stage IV disease remains unclear. A better understanding of how tumor size influences outcomes in metastatic disease could improve prognostic assessment, guide treatment selection, and shape future research priorities.

Based on these considerations, we hypothesized that very small primary tumors with extensive nodal involvement may represent a more aggressive biological phenotype in stage IV breast cancer than previously appreciated. To explore this, we analyzed BCSM according to tumor size stratified by LN status and examined tumor size–nodal interactions across four molecular subtypes. To ensure adequate representation of stage IV cases with small tumors, we utilized the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.

Materials and Methods

Patients

Data for this study were sourced from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, an open-access resource that compiles information from 18 population-based cancer registries with high reporting completeness. All data were publicly available, deidentified, and exempt from Institutional Review Board oversight.

Eligible patients were identified using SEER*Stat software (version 8.15; Surveillance Research Program, National Cancer Institute, www.seer.cancer.gov/seerstat) according to the following criteria: female sex, pathologically confirmed invasive ductal carcinoma, unilateral breast cancer, T1–T2 stage, a single primary site, stage IV disease, and known age at diagnosis. HER2/neu status is recorded in SEER only from 2010 onward, and to allow sufficient follow-up, patients diagnosed after 2015 were excluded. Consequently, this study included patients diagnosed between 2010 and 2015. Pathological classification followed the International Classification of Disease for Oncology, Third Edition, with infiltrating duct carcinoma coded as 8500.

The SEER database does not capture chemotherapy or endocrine therapy data; thus, these variables were not included in the analysis. Tumors were classified into molecular subtypes based on hormone receptor and HER2 status: hormone receptor-positive/HER2− (luminal A), hormone receptor-positive/HER2+ (luminal B), hormone receptor-negative/HER2+ (HER2-enriched), and hormone receptor-negative/HER2− (triple-negative breast cancer, TNBC). Tumor size and nodal status were analyzed jointly across T and N stages: T1a/T1bN0, T1a/T1bN1, T1a/T1bN2+, T1cN0, T1cN1, T1cN2+, T2N0, T2N1, and T2N2+ with T1a and T1b combined to ensure sufficient sample size.

The primary outcome was breast cancer-specific mortality (BCSM), defined as the interval from diagnosis to death from breast cancer. Deaths from other causes were censored at the date of death. Access to SEER data was granted under reference number 17297-Nov2018. The study protocol received ethical approval from the Ethical Committee Review Board of Fudan University Shanghai Cancer Center.

Statistical analysis

Continuous variables were analyzed using independent t-tests, while categorical variables were compared with either the chi-square test or Fisher's exact test, as appropriate. Risk factors for breast cancer-specific mortality (BCSM) were evaluated using both univariate and multivariate Cox proportional hazards models, with

results expressed as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Breast cancer-specific survival was visualized using Kaplan–Meier curves, and differences between groups were assessed with the log-rank test. BCSM at 1, 2, and 3 years was calculated, with smoothing applied via the Lowess method to account for variability in the CIs. Statistical analyses were performed using SPSS (v19.0; SPSS Inc.), SAS (v9.4; SAS Institute, Cary, NC), and R (v3.1.0; Vienna, Austria; http://www.R-project.org). All tests were two-sided, and a p-value of less than 0.05 was considered indicative of statistical significance.

Results and Discussion

Clinicopathologic patient parameters

A total of 5,340 eligible female patients were included in the study, with a median follow-up of 24.0 months (range, 0–83 months). By the end of follow-up, 1,933 patients (37.3%) had died from breast cancer, while 1,148 (21.5%) had died from other causes. **Table 1** presents the cohort demographics stratified by T stage. All patients had primary tumors measuring between 1 and 20 mm. Among the cohort, 408 patients (7.6%) had T1a/T1b tumors, 1,150 (21.5%) had T1c tumors, and 3,782 (70.8%) had T2 tumors. Tumor size was significantly associated with N stage, tumor grade, HER2 status, molecular subtype, presence of brain and lung metastases, cause of death, and receipt of surgery.

Compared with patients with T1c or T2 tumors, those with T1a/T1b tumors had fewer lymph node metastases (N0 stage: 54.7% vs. 44.3% vs. 28.8%; p < .0001), lower proportions of high-grade or undifferentiated tumors lower rates of brain (88.2% vs. 90.7% vs. 92.5%; p = .0052) and lung metastases (67.4% vs. 75.2% vs. 70%; p = .0048), less frequent HER2 amplification (23.5% vs. 27.1% vs. 28.7%; p = .0287), and a smaller proportion of high-grade or undifferentiated tumors (32.4% vs. 38.7% vs. 47.7%; p < .0001) Additionally, patients with T1a/T1b tumors were more likely to undergo local regional surgery (65.4% vs. 60.3% vs. 58%; p = .0288), and deaths in this group were less frequently attributable to breast cancer (27.2% vs. 30.9% vs. 40.4%; p < .0001).

Table 1. Baseline patient characteristics stratified by T stage

Characteristic	T1a/T1b (n = 408), n (%)	Total (n = 5,340), n (%)	T2 (n = 3,782), n (%)	T1c (n = 1,150), n (%)	p value[a]
Year of diagnosis					.8161
2010–2012	194 (47.5)	2,556 (47.9)	1,802 (47.6)	560 (48.7)	
2013–2015	214 (52.5)	2,784 (52.1)	1,980 (52.4)	590 (51.3)	
Age, years					.0934
≤35	33 (8.1)	434 (8.1)	322 (8.5)	79 (6.9)	
36–65	205 (50.2)	2,848 (53.3)	2,042 (54.0)	601 (52.3)	
>65	170 (41.7)	2,058 (38.5)	1,418 (37.5)	470 (40.9)	
Race					.2354
White	312 (76.5)	4,166 (78.0)	2,934 (77.6)	920 (80.0)	
Black	68 (16.7)	774 (14.5)	545 (14.4)	161 (14.0)	
Other[b]	28 (6.9)	391 (7.3)	296 (7.8)	67 (5.8)	
Unknown	0 (0.0)	9 (0.2)	7 (0.2)	2 (0.2)	
N stage					**<.0001**
N0	223 (54.7)	1,822 (34.1)	1,089 (28.8)	510 (44.3)	
N1	141 (34.6)	2,426 (45.4)	1,822 (48.2)	463 (40.3)	
N2+	44 (10.8)	1,092 (20.4)	871 (23.0)	177 (15.4)	
ER status					.1325
Positive	295 (72.3)	4,022 (75.3)	2,843 (75.3)	884 (76.9)	
Negative	99 (24.3)	1,210 (22.7)	868 (22.7)	243 (21.1)	
Unknown	14 (3.4)	108 (2.0)	71 (2.0)	23 (2.0)	
Grade					**<.0001**
I	67 (16.4)	382 (7.2)	216 (5.7)	99 (8.6)	
II	159 (39.0)	2,111 (39.5)	1,458 (38.6)	494 (43.0)	
III and UD	132 (32.4)	2,381 (44.6)	1,804 (47.7)	445 (38.7)	

Unknown	50 (12.3)	466 (8.7)	304 (8.0)	112 (9.7)	
HER2 status[c]					**.0287**
Amplification	96 (23.5)	1,494 (28.0)	1,086 (28.7)	312 (27.1)	
Not amplification	289 (70.8)	3,662 (68.6)	2,575 (68.1)	798 (69.4)	
Unknown	23 (5.6)	184 (3.4)	121 (3.2)	40 (3.5)	
PR					.3278
Positive	248 (60.8)	3,295 (61.7)	2,334 (61.7)	713 (62.0)	
Negative	145 (35.5)	1,924 (36.0)	1,370 (36.2)	409 (35.6)	
Unknown	15 (3.7)	121 (100.0)	78 (64.5)	28 (2.4)	
Surgery					**.0288**
Yes	267 (65.4)	3,154 (59.1)	2,194 (58.0)	693 (60.3)	
No	141 (34.6)	2,162 (40.5)	1,570 (41.5)	451 (39.2)	
Unknown	0 (0.0)	24 (0.4)	18 (0.5)	6 (0.5)	
Subtype					.2354
Luminal A	231 (56.6)	2,960 (55.4)	2,079 (55.0)	650 (56.5)	
Luminal B	58 (14.2)	939 (17.6)	687 (18.2)	194 (16.9)	
HER2	27 (6.6)	407 (7.6)	299 (7.9)	81 (7.0)	
TNBC	57 (14.0)	691 (12.9)	489 (12.9)	145 (12.6)	
Unknown	35 (8.6)	343 (6.4)	228 (6.0)	80 (7.0)	
Brain metastases					**.0052**
No	360 (88.2)	4,903 (91.8)	3,500 (92.5)	1,043 (90.7)	
Yes	40 (9.8)	328 (6.1)	206 (5.4)	82 (7.1)	
Unknown	8 (2.0)	109 (2.0)	76 (2.0)	25 (2.2)	
Bone metastases					.9580
No	155 (38.0)	1,955 (36.6)	1,377 (36.4)	423 (36.8)	
Yes	248 (60.8)	3,322 (62.2)	2,359 (62.4)	715 (62.2)	
Unknown	5 (1.2)	63 (1.2)	46 (1.2)	12 (1.0)	
Lung metastases					**.0048**
No	275 (67.4)	3,789 (71.0)	2,649 (70.0)	865 (75.2)	
Yes	124 (30.4)	1,435 (26.9)	1,051 (27.8)	260 (22.6)	
Unknown	9 (2.2)	116 (2.2)	82 (2.2)	25 (2.2)	
Liver metastases					.4879
No	304 (74.5)	3,882 (72.7)	2,739 (72.4)	839 (73.0)	
Yes	96 (23.5)	1,369 (25.6)	986 (26.1)	287 (25.0)	
Unknown	8 (2.0)	89 (1.7)	57 (1.5)	24 (2.1)	
Cause of death					**<.0001**
Alive	122 (29.9)	2,199 (41.2)	1,622 (42.9)	455 (39.6)	
Breast cancer	111 (27.2)	1,993 (37.3)	1,527 (40.4)	355 (30.9)	
Other	175 (42.9)	1,148 (21.5)	633 (16.7)	340 (29.6)	
Number of involved sites					.1655
0[d]	49 (12.0)	664 (12.4)	450 (11.9)	165 (14.3)	
1	245 (60.0)	3,229 (60.5)	2,288 (60.5)	696 (60.5)	
2	80 (19.6)	1,063 (19.9)	779 (20.6)	204 (17.7)	
3	25 (6.1)	313 (5.9)	220 (5.8)	68 (5.9)	
4	7 (1.7)	40 (0.7)	24 (0.6)	9 (0.8)	
Unknown	2 (0.5)	31 (0.6)	21 (0.6)	8 (0.7)	

[a] p-value from the χ^2 test comparing the T1c / T1b/ T1a/, and T2 groups.

[b] Includes Asian/Alaskan Native/ Pacific Islander/and American Indian populations.

[c] HER2 amplification was defined as either 3+ by immunohistochemistry or confirmed gene amplification via fluorescence in situ hybridization.

[d] Only organ metastases were considered as involved sites; distant lymph node metastases were not counted.

Abbreviations**:** PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; UD, undifferentiated; ER, estrogen receptor; TNBC, triple-negative breast cance

Interaction of primary tumor size and lymph node involvement with respect to breast cancer-specific mortality

On univariate testing, several factors were linked to higher breast cancer-specific mortality (BCSM): diagnosis between 2010 and 2012, African American ethnicity, age exceeding 65 years, poorly differentiated or undifferentiated histology (grade III), negative estrogen receptor (ER) expression, negative progesterone receptor (PR) expression, negative HER2 expression, triple-negative subtype, metastases to the brain, lack of surgical intervention, lungs or liver, and the presence of at least two distant metastatic sites **(Table 2).**

For patients with T1 tumors, when T1a/T1bN0 served as the reference category, comparable BCSM was observed in the following subgroups: T1cN0 (HR, 1.204; 95% CI, 0.886–1.636; p = .235), T1cN1 (HR, 1.175; 95% CI, 0.865–1.596; p = .301), T1a/T1bN1 (HR, 1.119; 95% CI, 0.739–1.695; p = .595), T1cN2+ (HR, 0.907; 95% CI, 0.619–1.328; p = .615), and T1a/T1bN2 (HR, 1.178; 95% CI, 0.666–2.083; p = .573).

Across nodal categories N0, N1, and N2+, T2 tumors showed increased BCSM relative to T1a/T1b tumors (1.590 vs. 1.119; HR, 1.547 vs. 1; 1.423 vs. 1.178; p < .05), but T1c tumors did not demonstrate elevated BCSM compared with T1a/T1b tumors (p > .1).

Individuals with ER/PR-negative disease experienced substantially greater BCSM than those with ER+/PR+ disease, and HER2-negative cases had higher BCSM than HER2-positive cases. Broadly, triple-negative breast cancer carried a markedly elevated risk of BCSM versus the luminal A subtype (95% CI, 2.518–3.177; HR, 2.828; p < .001).

In multivariable modeling, independent correlates of BCSM included race, age at diagnosis, histologic grade, molecular subtype, brain or liver metastases, and whether surgery was performed **(Table 3).** Survival outcomes for luminal A and HER2-enriched subtypes were alike, while triple-negative cases showed markedly poorer BCSM relative to luminal A (95% CI, 2.33–3.014; HR, 2.65; p < .0001). Patients aged over 65 years had worse BCSM compared to younger patients (95% CI, 1.4–1.993; HR, 1.671; p < .0001).

Among T2 tumors, N2+ involvement conferred higher BCSM than N1 or N0 status (HR, 1.738 vs. 1.538 vs. 1.482; p < .05). Conversely, in T1 tumors, BCSM did not differ based on finer tumor size categories or degree of nodal disease (HR, 0.989 vs. 1.176 vs. 1.599 vs. 1.107 vs. 1.122; p > .05).

Kaplan-Meier estimates were used to assess BCSM according to tumor size and nodal status, with distinct survival plots created for every T-N combination **(Figure 1).** T1 subgroups exhibited equivalent BCSM across T1cN0, T1a/T1bN1, T1cN1, T1a/T1bN0, T1cN2, and T1a/T1bN2 **(Figure 1a)**; p > .05). Similarly, T2 subgroups showed no differences in BCSM between T2N0, T2N1, and T2N2+ **(Figure 1b);** (p > .05).

In cases with primary tumors under 50 mm, 1-year and 2-year BCSM rates were consistent across sizes **(Figure 2a and 2b)**, although 3-year BCSM trended marginally higher for the smallest tumors relative to those around 20 mm **(Figure 2c)**.

Table 2. Univariate analysis on breast cancer-specific mortality

Variable	Hazard ratio (95% CI)	SE	p value
Race			
White (ref.)			
Black	1.406 (1.250–1.582)	0.060	**<.0001**
Other	0.833 (0.695–0.998)	0.092	**.0480**
Unknown	0.000 (0.000–53.736)	46.683	.8480
Year of diagnosis			
2010–2012 (ref.)			
2013–2015	0.958 (0.871–1.053)	0.049	.3750
Age, years			
≤35 (ref.)			
36–65	1.116 (0.944–1.319)	0.085	.1990
>65	1.503 (1.267–1.783)	0.087	**<.0001**
ER status			
Positive (ref.)			
Negative	2.054 (1.865–2.261)	0.049	**<.0001**
Unknown	1.802 (1.335–2.434)	0.153	**<.0001**
Grade			

I (ref.)			
II	1.663 (1.326–2.086)	0.116	**<.0001**
III and UD	2.359 (1.888–2.947)	0.114	**<.0001**
Unknown	2.405 (1.784–2.979)	0.131	**<.0001**
PR			
Positive (ref.)			
Negative	1.998 (1.827–2.184)	0.046	**<.0001**
Unknown	1.651 (1.233–2.212)	0.149	**.0010**
Subtype			
Luminal A (ref.)			
Luminal B	0.903 (0.793–1.028)	0.066	.1240
HER2	1.049 (0.881–1.250)	0.089	.5890
TNBC	2.828 (2.518–3.177)	0.059	**<.0001**
Unknown	1.316 (1.095–1.581)	0.094	**.0030**
HER2 status[a]			
Amplification (ref.)			
Not amplification	1.263 (1.140–1.399)	0.052	**<.0001**
Unknown	1.348 (1.044–1.740)	0.130	**.0220**
Surgery			
No (ref.)			
Yes	0.511 (0.466–0.562)	0.048	**<.0001**
Unknown	1.089 (0.602–1.972)	0.303	.7770
Brain metastases			
No (ref.)			
Yes	2.783 (2.399–3.230)	0.076	**<.0001**
Unknown	1.409 (1.075–1.848)	0.138	**.0130**
Bone metastases			
No (ref.)			
Yes	1.021 (0.931–1.120)	0.047	.6530
Unknown	1.599 (1.154–2.216)	0.167	**.0050**
Lung metastases			
No (ref.)			
Yes	1.516 (1.378–1.669)	0.049	**<.0001**
Unknown	1.653 (1.276–2.141)	0.132	**<.0001**
Liver metastases			
No (ref.)			
Yes	1.844 (1.678–2.026)	0.048	**<.0001**
Unknown	1.806 (1.361–2.395)	0.144	**<.0001**
Tumor nodal interaction			
T1a/T1bN0 (ref.)			
T1cN0	1.204 (0.886–1.636)	0.156	.2350
T2N0	1.547 (1.170–2.045)	0.142	**.0020**
T1a/T1bN1	1.119 (0.739–1.695)	0.212	.5950
T1cN1	1.175 (0.865–1.596)	0.156	.3010
T2N1	1.590 (1.212–2.086)	0.138	**.0010**
T1a/T1bN2+	1.178 (0.666–2.083)	0.291	.5730
T1cN2+	0.907 (0.619–1.328)	0.195	.6150
T2N2+	1.423 (1.074–1.887)	0.144	**.0140**
Number of involved sites			
0[b] (ref.)			
1	1.138 (0.975–1.329)	0.079	.1010
2	2.218 (1.877–2.621)	0.085	**<.0001**

3	3.240 (2.629–3.992)	0.107	**<.0001**
4	4.396 (2.897–6.673)	0.213	**<.0001**
Unknown	2.019 (1.593–2.558)	0.121	**<.0001**

[a]HER2 status was considered positive if immunohistochemistry showed a 3+ result or if gene amplification was confirmed by fluorescence in situ hybridization.

[b]Only metastases to organs were included in the count of involved sites; metastases limited to distant lymph nodes were excluded.

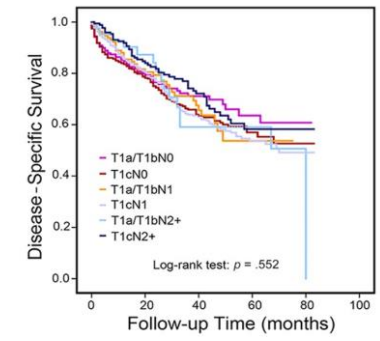
Abbreviations: HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; CI, confidence interval; UD, undifferentiated; PR, progesterone receptor; ER, estrogen receptor.

Table 3. Multivariate analysis of breast cancer-specific mortality

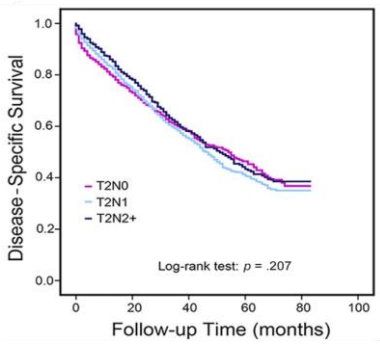
Variable	Hazard ratio (95% CI)	p value
Age, years		
≤35 (ref.)		
36–65	1.152 (0.972–1.365)	.1020
>65	1.671 (1.400–1.993)	**<.0001**
Race		
White (ref.)		
Black	1.308 (1.160–1.475)	**<.0001**
Other	0.892 (0.743–1.071)	.2200
Unknown	0.000 (0.000–38.445)	.8420
Subtype		
Luminal A (ref.)		
Luminal B	0.758 (0.662–0.868)	**<.0001**
HER2	0.874 (0.728–1.050)	.1510
TNBC	2.650 (2.330–3.014)	**<.0001**
Unknown	1.137 (0.944–1.370)	.1760
Grade		
I (ref.)		
II	1.511 (1.203–1.899)	**.0004**
III and UD	2.066 (1.640–2.604)	**<.0001**
Unknown	1.757 (1.354–2.280)	**<.0001**
Bone metastases		
No (ref.)		
Yes	1.112 (0.830–1.489)	.4760
Unknown	1.255 (0.764–2.060)	.3700
Surgery		
No (ref.)		
Yes	0.511 (0.461–0.566)	**<.0001**
Unknown	1.048 (0.577–1.905)	.8780
Liver metastases		
No (ref.)		
Yes	1.574 (1.178–2.103)	**.0020**
Unknown	1.309 (0.858–1.997)	.2110
Brain metastases		
No (ref.)		
Yes	2.115 (1.562–2.863)	**<.0001**
Unknown	0.936 (0.621–1.412)	.7530
Number of involved sites		
0[b] (ref.)		
1	1.042 (0.755–1.438)	.8030
2	1.404 (0.785–2.512)	.2530
3	1.442 (0.611–3.401)	.4040

4	0.971 (0.298–3.161)	.9610
Unknown	1.428 (0.749–2.722)	.2790
Tumor nodal interaction		
T1a/T1bN0 (ref.)		
T1cN0	1.176 (0.864–1.599)	.3020
T2N0	1.482 (1.120–1.961)	**.0060**
T1a/T1bN1	0.989 (0.652–1.499)	.9570
T1cN1	1.107 (0.814–1.505)	.5180
T2N1	1.538 (1.170–2.021)	**.0020**
T1a/T1bN2+	1.599 (0.901–2.840)	.1090
T1cN2+	1.122 (0.764–1.649)	.5570
T2N2+	1.738 (1.305–2.314)	**.0002**
Lung metastases		
No (ref.)		
Yes	1.085 (0.810–1.454)	.5840
Unknown	0.971 (0.642–1.469)	.8880

[a]The count of involved sites included only metastases to organs; involvement of distant lymph nodes was not considered.
[b]HER2 positivity was defined as either a 3+ result on immunohistochemistry or the presence of gene amplification detected via fluorescence in situ hybridization.
Abbreviations: CI, confidence interval; UD, undifferentiated; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2.

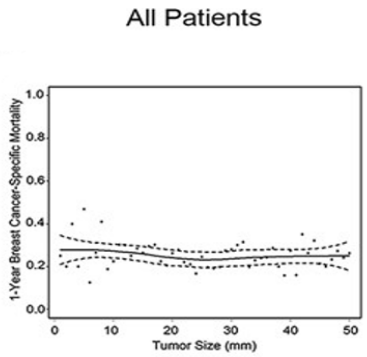


a)

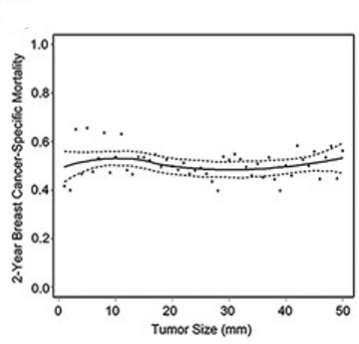


b)

Figure 1. Breast cancer-specific survival based on tumor size, analyzed according to lymph node metastasis status. (a) Cohort with T1 tumors, p = .552. (b) Cohort with T2 tumors, p = .207.



a)



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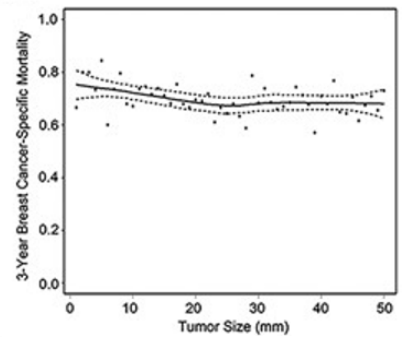
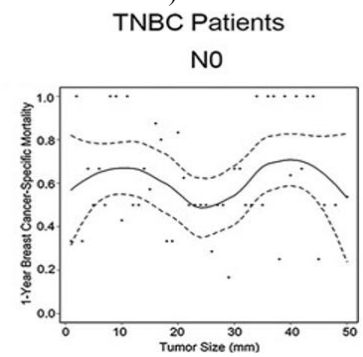


c)



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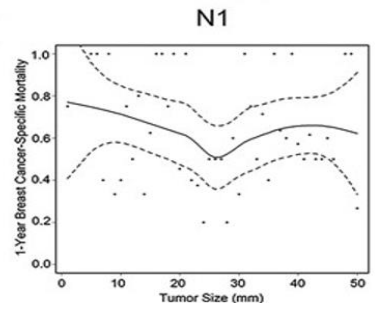

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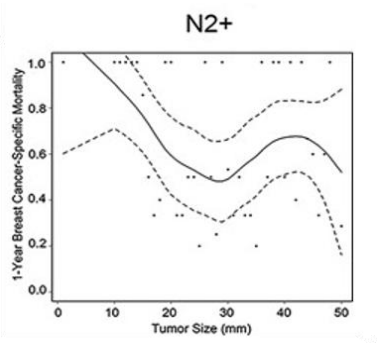

f)

Figure 2. Breast cancer-specific mortality (BCSM) at one, two, and three years, stratified by tumor size. (a) One-year BCSM for all patients. (b) Two-year BCSM for all patients. (c) Three-year BCSM for all patients. (d) One-year BCSM for patients with N0 TNBC. (e) One-year BCSM for patients with N1 TNBC. (f) One-year BCSM for patients with N2+ TNBC.

Abbreviation: Triple-negative breast cancer, TNBC

Assessment of lymph node and tumor size effects by breast cancer subtype

The relationship between tumor size, lymph node (LN) involvement, and breast cancer-specific mortality (BCSM) was further evaluated within each molecular subtype **(Table 4).** Kaplan–Meier analyses indicated that patients with metastatic triple-negative breast cancer (TNBC) consistently experienced poorer BCSM than patients with other subtypes across several subgroups, including T2N0, T1cN1, T1a/T1bN0, T2N2+, T1cN0, T2N1, T1cN2+, and T1a/T1bN2+.

Notably, small TNBC tumors with minimal nodal involvement (T1a/T1bN1) had similar BCSM outcomes as luminal A, luminal B, and HER2-amplified cancers (log-rank p = .663). For luminal A tumors, BCSM did not differ between T1 tumors regardless of nodal status, whereas T2 tumors were associated with worse outcomes. Among luminal B patients, BCSM remained consistent across different combinations of tumor size and nodal involvement. A comparable trend was observed in HER2-amplified patients.

In the node-negative TNBC group, BCSM appeared unaffected by tumor size **(Table 4),** with no clear increase in mortality as tumor size grew **(Figure 2d).** For N1 TNBC, patients with T2 tumors exhibited higher BCSM than those with T1c or T1a/T1b tumors ($p < .05$; HR: 2.271 vs. 1.619 vs. 0.860). Interestingly, in the N1 subgroup with tumors under 25 mm, one-year BCSM slightly decreased with increasing tumor size **(Figure 2e).**

For patients with N2+ TNBC, those with the smallest tumors (T1a/T1b) experienced the highest BCSM compared to T1c and T2 tumors (p = .004, p = .204, and p = .027; HR: 5.847 vs. 1.778 vs. 2.254; respectively). In the N2+ subgroup with tumors smaller than 30 mm, one-year BCSM decreased significantly as tumor size increased **(Figure 2f)**.

Table 4. Breast cancer-specific mortality by tumor size and lymph node status, stratified by molecular subtype.

Stage	Luminal A		Luminal B		TNBC		HER2	
	HR (95% CI)	p value	HR (95% CI)	HR (95% CI)	p value	p value	HR (95% CI)	p value
T1cN0	1.367 (0.858–2.179)	.188	0.821 (0.383–1.763)	0.776 (0.239–2.515)	.672	.614	1.686 (0.788–3.611)	.178
T1a/T1bN0 (ref.)	1.000			1.000	1.000		1.000	
T2N0	1.782 (1.158–2.744)	**.009**	1.196 (0.605–2.363)	0.588 (0.214–1.617)	.303	.607	1.742 (0.850–3.571)	.130
T1cN1	1.465 (0.918–2.338)	.110	0.504 (0.234–1.088)	0.439 (0.146–1.322)	.143	.081	1.619 (0.753–3.482)	.218
T1a/T1bN1	1.335 (0.725–2.459)	.354	0.638 (0.207–1.967)	0.627 (0.162–2.433)	.500	.435	0.860 (0.314–2.356)	.769
T1a/T1bN2+	1.857 (0.794–4.341)	.153	0.600 (0.127–2.825)	0.312 (0.037–2.636)	.285	.518	5.847 (1.738–19.672)	**.004**
T2N1	1.862 (1.22–2.841)	**.004**	0.869 (0.450–1.681)	0.532 (0.204–1.386)	.196	.677	2.271 (1.127–4.575)	**.022**
T2N2+	1.957 (1.258–3.047)	**.003**	1.180 (0.594–2.345)	0.619 (0.227–1.689)	.349	.636	2.254 (1.094–4.643)	**.027**
T1cN2+	1.221 (0.677–2.203)	.508	0.726 (0.271–1.951)	0.425 (0.123–1.471)	.176	.526	1.778 (0.732–4.320)	.204

[a]HER2 positivity was determined either by a 3+ result on immunohistochemistry or by detection of gene amplification using fluorescence in situ hybridization.

[b]Only organ metastases were considered when counting involved sites; metastases in distant lymph nodes were not included.

Abbreviations: HER2, human epidermal growth factor receptor 2; CI, confidence interval; TNBC, triple-negative breast cancer; HR, hazard ratio .

This study aimed to investigate whether tumor size and lymph node (LN) involvement interact in predicting breast cancer-specific mortality (BCSM) in stage IV breast cancer. We hypothesized that stage IV breast cancers with very small primary tumors (T1a/T1b) but significant LN metastases would be associated with aggressive outcomes. After adjusting for known prognostic factors, we found that patients with T1a/T1bN2+ tumors had comparable BCSM to those with T1cN2+ tumors (HR, 1.599 vs. 1.122; $p > .05$). A similar pattern was observed in patients with less extensive nodal involvement.

However, in TNBC, patients with T1a/T1bN2+ tumors had significantly worse BCSM than those with T1cN2+ or T2N2+ tumors. For tumors under 50 mm, one- and two-year BCSM for smaller tumors were similar to larger tumors, whereas three-year BCSM appeared slightly higher in smaller tumors compared with 20 mm tumors **(Figure 2)**, likely driven by the high mortality in the T1a/T1bN2+ TNBC subgroup. This suggests that in stage IV breast cancer, smaller tumor size does not necessarily indicate better prognosis. While the conventional model suggests that metastatic potential arises gradually through accumulated mutations [11], our findings indicate that very small TNBCs with extensive LN and distant metastases may represent a subset with inherently higher invasive and metastatic potential. These results align with previous studies [13, 14], supporting the idea that in some cancers, early biological characteristics may dictate metastatic ability more than tumor growth itself.

Our study adds to growing evidence that certain breast cancer subtypes, such as TNBC, have a high metastatic propensity and poor prognosis even when primary tumors are small [10, 12]. Prior research has shown that basal-like tumors often present as interval cancers, developing rapidly between screening interventions [15]. Basal-like tumors exhibit the highest proliferation-related gene expression and Ki67 indices among all subtypes [16, 17]. Moreover, basal-like and BRCA1-related tumors frequently consist of densely packed solid sheets with minimal stroma and tubule formation, features that favor rapid progression and distant metastasis [18]. These characteristics correspond with our observation that TNBC exhibits worse BCSM than other metastatic subtypes. Small TNBCs with significant nodal disease demonstrated particularly aggressive clinical behavior. It is plausible that T1a/T1bN2+

TNBCs possess enhanced ability to invade local tissue, enter lymphatic or hematogenous circulation, survive in the bloodstream, and establish metastatic sites. Compared with T2N2+ TNBCs, the T1a/T1bN2+ subgroup suggests that metastatic potential may be acquired early during tumor development [19], rather than accumulating with tumor growth [11]. Unlike T1a/T1bN0 TNBCs, T1a/T1bN2+ TNBCs appear capable of metastasizing through multiple routes and efficiently colonizing lymph nodes.

Our findings also support population-based studies indicating that younger women with stage IV breast cancer generally have better survival even after adjustment for other prognostic factors [20]. In our cohort, age over 65 was independently associated with worse BCSM (HR, 1.671; $p < .0001$). Additionally, involvement of brain or liver was confirmed as an independent negative prognostic factor (HR, 2.115 and 1.574; $p < .0001$ and $p = .002$, respectively) [21, 22]. Black race was also independently linked to increased BCSM (HR, 1.308; $p < .0001$), consistent with prior studies [23, 24].

These findings suggest that very small tumors with extensive nodal involvement may indicate intrinsic biological aggressiveness in stage IV TNBC. With the emergence of molecular subtyping by gene expression profiling, tumor biology has become increasingly recognized as a key predictor of clinical outcomes [25–27]. While some of our results might reflect limitations in adjusting for systemic therapy, this is unlikely to fully explain the elevated mortality observed in T1a/T1bN2+ TNBCs. Our data imply that additional biomarkers related to metastatic potential, yet to be identified, may further refine prognostic assessments. The presence of extensive LN involvement with a very small primary tumor suggests early acquisition of metastatic ability and rapid progression in T1a/T1bN2+ TNBCs. Future studies focusing on this subgroup could uncover genetic or molecular drivers of aggressive behavior, potentially guiding targeted therapies. Clinically, these patients warrant aggressive treatment despite small tumor size, as their risk of breast cancer-related death remains substantial.

This study has several limitations. First, HER2 status is only recorded in the SEER database from 2010 onward, so we included only cases diagnosed after this year, reducing the sample size. Subgroup stratification further limited statistical power, resulting in wide confidence intervals and reduced ability to detect meaningful differences. Additionally, T1a and T1b tumors were combined due to small numbers. Second, the SEER database lacks information on systemic therapy, which could not be accounted for as a confounding factor. Third, the retrospective design may have introduced bias into our findings.

Conclusion

Our study demonstrated that stage IV breast cancers with small primary tumors did not show a significant difference in BCSM compared with larger tumors. Notably, very small TNBCs with extensive regional lymph node involvement exhibited substantially higher BCSM than larger tumors, indicating that small tumor size combined with severe nodal disease may reflect an inherently aggressive tumor biology. Given the poor outcomes associated with T1a/T1bN2+ TNBCs, there may be an urgent need for more tailored treatment strategies for these patients. If confirmed in other datasets, future studies should investigate the genetic and molecular factors driving the aggressive behavior of T1a/T1bN2+ TNBCs.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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