Subdivision of M1 Stage for De Novo Metastatic Breast Cancer to Better Predict Prognosis and Response to Primary Tumor Surgery

Caijin Lin, MMed*; Jiayi Wu, MD*; Shuning Ding, MMed*; Chihwan Goh, MMed; Lisa Andriani, MMed; Shuangshuang Lu, MD; Kunwei Shen, MD, PhD; and Li Zhu, MD, PhD

ABSTRACT

Background: Patients with de novo metastatic breast cancer (MBC) constitute a heterogeneous group with different clinicopathologic characteristics and survival outcomes. Despite controversy regarding its prognostic value, primary tumor surgery may improve survival for selected patients. **Patients and Methods:** Patients with de novo MBC were identified using the SEER database and were then divided randomly into training and validation sets. A Fine-Gray competing risks model was developed to identify the variables associated with increased cancer-specific mortality in the training set. The M1 subdivision system was established based on the independent prognostic factors. Cumulative incidence curves were estimated and compared using Gray's test. **Results:** Involvement of brain or liver and number of metastatic sites were identified as independent prognostic factors in multivariate analysis. The M1 category was subdivided into 3 subcategories: M1a, single site involvement except brain and liver; M1b, liver involvement only, or multiple site involvement except brain and liver; and M1c, brain involvement regardless of number of metastatic sites, or liver and other sites involvement except brain (M1b vs M1a: subdistribution hazard ratio [SHR], 1.48; 95% CI, 1.29–1.68; M1c vs M1a: SHR, 2.45; 95% CI, 2.18–2.75). Patients with the M1a subtype benefited most from primary tumor surgery in the adjusted competing risks model (M1a: SHR, 0.57; 95% CI, 0.48–0.67, M1b: SHR, 0.62; 95% CI, 0.47–0.83, and M1c: SHR, 0.59; 95% CI, 0.44–0.80), whereas benefits conferred by treatment with chemotherapy alone increased with the upstaging of metastatic disease (M1a: SHR, 0.72; 95% CI, 0.62–0.83, M1b: SHR, 0.54; 95% CI, 0.44–0.68, and M1c: SHR, 0.53; 95% CI, 0.45–0.61). **Conclusions:** Subdivision of M1 stage facilitates prognosis prediction and treatment planning for patients with de novo MBC. Treatment offered should be decided in a coordinated multidisciplinary setting. Primary tumor surgery may play an important role in the management of selected patients.

J Natl Compr Canc Netw 2019;17(12):1521–1528
doi: 10.6004/jnccn.2019.7332

Background

Approximately 5% to 10% of patients with newly diagnosed breast cancer have distant metastases, with 5-year cancer-specific mortality (CSM) ranging from 60% to 74% among different races/ethnicities.¹ Median overall survival of patients with de novo metastatic breast cancer (MBC) is reported to be 12 to 32 months, suggesting that these patients constitute a heterogeneous group with a wide range of survival.^{2–6} Consequently, it is not appropriate to assign these patients a “catch-all” classification.

Tumor (T), node (N), metastasis (M) classification and staging of malignancy presents the anatomic extent of cancer. Of the 75 types of malignancy described by the TNM staging system, appropriately 20 include further subdivisions of the M1 category, such as prostate and lung cancers.^{7,8} However, the staging system for breast cancer uses only “M1” to describe metastatic disease. Therefore, all patients with de novo MBC are considered to have the same prognostic stage, regardless of histologic grade and HER2, estrogen receptor (ER), and progesterone receptor (PR) status. Hence, further subdivision of the M1 category for metastatic disease is of clinical importance for accurate prognosis prediction and personalized treatment planning.^{9–11}

De novo MBC is considered incurable but treatable. Generally, systemic therapy is viewed as the mainstay of treatment.¹² Primary tumor surgery is considered in selected patients, mostly in the palliative setting for those with impending complications, such as fungation and skin ulceration.^{13,14} Considerable controversy remains regarding the prognostic value of nonpalliative surgery for primary tumor. Two randomized trials have suggested caution in selecting patients for locoregional surgery due to little survival gain (ClinicalTrials.gov

Comprehensive Breast Health Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China.

*Contributed equally.

See JNCCN.org for supplemental online content.

identifiers: NCT00193778, NCT00941759), whereas a Turkish trial revealed potential benefits, especially in patients with solitary bone metastasis.⁵ However, the results are not conclusive enough due to inconsistency, and it remains uncertain which subgroup of patients would respond well to either monotherapies or combination therapy. To address this uncertainty, we performed a population-based study and subdivided patients with de novo MBC into different subcategories to stratify prognostication and help treatment planning.

Patients and Methods

Database and Case Selection

Population-based data were obtained from the SEER database, which covers approximately 28% of the US population.¹⁶ SEER collects and reports data on patient demographics, primary tumor sites and morphology, tumor stage at diagnosis, first treatment course, and survival outcomes.

Patients with de novo MBC diagnosed in 2010 through 2014 were identified using SEER*Stat software (version 8.3.5; seer.cancer.gov/seerstat). Breast cancer was identified using ICD-O-3 codes (C50.0–C50.6, C50.8, and C50.9). Only patients diagnosed with their first malignancy were included. All patients were >18 years of age. Patients with disease other than stage IV, unknown demographic characteristics and follow-up, or unknown involvement of bone, brain, liver, or lung, and those diagnosed at autopsy or via death certificate were excluded. Eligible patients were divided randomly into the training or validation sets using the basic R function *sample()*.

Statistical Analysis

Pearson chi-square tests were used to analyze categorical variables. The main outcomes were CSM (breast cancer–specific death [BCSD]) and all-cause mortality. CSM was compared by estimating cumulative incidence curves according to Gray's test.¹⁷ A Fine-Gray regression model was developed to estimate subdistribution hazard ratios (SHRs) for CSM.¹⁸ Cumulative incidence curves of all-cause mortality were estimated based on the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model using a backward stepwise approach was built to estimate the hazard ratios (HR) for all-cause mortality. Patients in the training set were divided into several groups according to the combination of the independent prognostic factors for CSM. Cumulative incidence rates for CSM in each group were estimated and compared, using a 2-sided *P* value of <.001 to ensure a significant difference in survival. Groups with significantly different prognosis were divided into different M1 subcategories.

In addition, multiple comparisons based on Gray's test and a Fine-Gray regression model were performed, with different treatment modalities used as the reference across M1 subcategories. To reduce the bias caused by no adjustment for use of radiotherapy (RT), endocrine therapy, and targeted anti-HER2 therapy, multiple comparisons were repeated in women who did not receive RT and in those with triple-negative breast cancer (TNBC) who did not receive RT.

All tests used 2-sided *P* values of <.05 suggesting statistical significance unless otherwise stated. Pearson Chi-square test and a Cox proportional hazards model were developed using SPSS Statistics, version 24 (IBM Corp). Kaplan-Meier method, Gray's test, and a Fine-Gray regression model were performed using R version 3.4.3 (R Foundation for Statistical Computing).

Results

Baseline Characteristics

Of the 312,041 patients diagnosed with breast cancer, 8,582 were identified with de novo MBC, including 4,291 each in the training or validation sets. In both sets, the most frequently involved metastatic sites were bone, lung, liver, and brain, and clinicopathologic characteristics were well-balanced. Detailed baseline characteristics are outlined in Table 1 and supplemental eTables 1, and 2 (available with this article at JNCCN.org).

Association Between Characteristics of Distant Metastases and CSM

Univariate analysis showed that involvement of brain, liver, or lung, and of multiple (>1 or >2) metastatic sites was associated with increased CSM. Multivariable analysis showed that involvement of brain (SHR, 2.13; 95% CI, 1.80–2.52; *P*<.001) and liver (SHR, 1.71; 95% CI, 1.51–1.95; *P*<.001) were independent prognostic factors. After adjusting for the same parameters, involvement of multiple (>1) metastatic sites remained a significant predictor of CSM (SHR, 1.28; 95% CI, 1.11–1.47; *P*<.001) (supplemental eTable 3). Additionally, we found that involvement of multiple (>1) metastatic sites was associated with increased CSM in the absence of brain involvement (*P*<.001) (supplemental eFigure 1A–C). However, no significant difference was observed when brain was involved (*P*>.05) (supplemental eFigure 1D–F).

Subdivision of M1 Category

Patients in the training set were divided into 5 groups according to the independent prognostic factors (see supplemental eTable 4 for comparisons among the 5 groups). Consequently, patients with de novo MBC were subdivided into 3 categories: M1a, involvement of a single site except brain or liver; M1b, liver involvement only,

Table 1. Baseline Patient Characteristics (N=8,582)

	Training Set n (%)	Validation Set n (%)	P Value
Age, y			.370
<41	376 (8.8)	423 (9.9)	
41–60	1,850 (43.1)	1,836 (42.8)	
61–80	1,695 (39.5)	1,662 (38.7)	
>80	370 (8.6)	370 (8.6)	
Marital status			.965
Unmarried	2,314 (53.9)	2,316 (54.0)	
Married	1,977 (46.1)	1,975 (46.0)	
Histologic grade			.122
Well-differentiated	306 (7.1)	322 (7.5)	
Moderately differentiated	1,803 (42.0)	1,771 (41.3)	
Poorly differentiated	2,135 (49.8)	2,170 (50.6)	
Undifferentiated	47 (1.1)	28 (0.7)	
AJCC T category			.979
T0	385 (9.0)	377 (8.8)	
T1	457 (10.7)	455 (10.6)	
T2	1,309 (30.5)	1,326 (30.9)	
T3	720 (16.8)	703 (16.4)	
T4	1,420 (33.1)	1,430 (33.3)	
AJCC N category			.657
N0	1,158 (27.0)	1,155 (26.9)	
N1	1,927 (44.9)	1,892 (44.1)	
N2	515 (12.0)	552 (12.9)	
N3	691 (16.1)	692 (16.1)	
Subtype			.099
HoR+/HER2–	2,554 (59.5)	2,491 (58.1)	
HoR+/HER2+	775 (18.1)	744 (17.3)	
HoR–/HER2+	387 (9.0)	409 (9.5)	
Triple-negative	575 (13.4)	647 (15.1)	
Bone involvement			.338
No	1,343 (31.3)	1,302 (30.3)	
Yes	2,948 (68.7)	2,989 (69.7)	
Brain involvement			.560
No	3,987 (92.9)	3,973 (92.6)	
Yes	304 (7.1)	318 (7.4)	
Liver involvement			.885
No	3,108 (72.4)	3,102 (72.3)	
Yes	1,183 (27.6)	1,189 (27.7)	
Lung involvement			.231
No	2,872 (66.9)	2,924 (68.1)	
Yes	1,419 (33.1)	1,367 (31.9)	

(continued)

Abbreviation: HoR, hormone receptor.

Table 1. Baseline Patient Characteristics (N=8,582) (cont.)

	Training Set n (%)	Validation Set n (%)	P Value
Number of metastatic sites			
Binary classifications 1			.837
1 site	2,854 (66.5)	2,845 (66.3)	
>1 site	1,437 (33.5)	1,446 (33.7)	
Binary classifications 2			.648
1 or 2 sites	3,919 (91.3)	3,907 (91.1)	
>2 sites	372 (8.7)	384 (8.9)	
Treatment modality			.843
None	1,326 (30.9)	1,345 (31.3)	
Surgery only	485 (11.3)	469 (10.9)	
Chemotherapy only	1,376 (32.1)	1,397 (32.6)	
Surgery + chemotherapy	1,104 (25.7)	1,080 (25.2)	

Abbreviation: HoR, hormone receptor.

or involvement of multiple sites except brain or liver; M1c, brain involvement regardless of number of metastatic sites, or involvement of liver and other sites except brain. Both the 3-year CSM and all-cause mortality rates increased across M1 subcategories (Figure 1A, 1D). In the adjusted competing risk model, the association of M1 subcategories with CSM remained significant (M1b vs M1a: SHR, 1.48; 95% CI, 1.29–1.68; $P<.001$, and M1c vs M1a: SHR, 2.45; 95% CI, 2.18–2.75; $P<.001$) (Table 2 and supplemental eTable 5). Additionally, the M1 subcategories were also associated with increased all-cause mortality (M1b vs M1a: SHR, 1.47; 95% CI, 1.30–1.66; $P<.001$, and M1c vs M1a: SHR, 2.38; 95% CI, 2.14–2.65; $P<.001$) (Table 2 and supplemental eTable 6).

Validation of M1 Category Subdivision

Validation of the M1 category subdivision system is described in supplemental eAppendix 1, eFigure 2, and eTables 5–8.

Associations of Treatment Modality and M1 Subcategories With Survival Outcomes

Cumulative incidence curves show the mortality reduction by primary tumor surgery, chemotherapy, or combination therapy across M1 subcategories (Figure 2A–C).

When the monotherapies were compared with no treatment in the whole population, primary tumor surgery remained a favorable prognostic factor in the adjusted competing risk model, especially for patients with M1a disease (M1a: SHR, 0.57; 95% CI, 0.48–0.67; $P<.001$, M1b: SHR, 0.62; 95% CI, 0.47–0.83; $P=.001$, and M1c: SHR, 0.59; 95% CI, 0.44–0.80; $P<.001$) (Table 3). Furthermore, patients with M1a disease benefited less

Figure 1. Cumulative incidence curves of (A–C) cancer-specific and (D–F) all-cause mortality for different M1 subcategories in the (A, D) training, (B, E) validation, and (C, F) whole sets. *P* values were estimated and compared based on Gray's test (A–C) or log-rank test (D–F). Abbreviations: BCSD, breast cancer-specific death; LG, log-rank.

from chemotherapy alone than those with M1b or M1c disease (M1a: SHR, 0.72; 95% CI, 0.62–0.83; $P < .001$, M1b: SHR, 0.54; 95% CI, 0.44–0.68; $P < .001$, and M1c: SHR, 0.53; 95% CI, 0.45–0.61; $P < .001$). Specifically, no significant difference in survival was seen between patients treated with surgery only and those treated with chemotherapy only, with the exception of patients with M1a disease, among whom those receiving chemotherapy only presented a worse prognosis (SHR, 1.27; 95% CI, 1.06–1.51; $P = .008$). As for the combined therapy, those receiving the combination exhibited the lowest SHR across M1 subcategories (M1a: SHR, 0.39; 95% CI, 0.34–0.46; $P < .001$, M1b: SHR, 0.46; 95% CI, 0.36–0.58, $P < .001$, and M1c: SHR, 0.32; 95% CI, 0.26–0.38; $P < .001$). However, for patients classified as M1b, the combination therapy provided similar benefits to monotherapies (combination vs surgery only: SHR, 0.73; 95% CI, 0.54–1.00; $P = .048$; combination vs chemotherapy only: SHR, 0.84; 95% CI, 0.68–1.03; $P = .094$).

Similar results were observed in patients with or without TNBC who did not receive RT. Cumulative incidence curves are presented in supplemental eFigure 3. Among patients who did not receive RT ($n = 5,584$), those classified as M1c who received chemotherapy only had a better prognosis than those undergoing surgery only (SHR, 0.69; 95% CI, 0.49–0.97; $P = .035$) (supplemental eTable 9). In patients with TNBC not receiving RT ($n = 808$), those receiving locoregional surgery presented similar prognosis to treatment-naïve patients (M1a: SHR, 0.94; 95% CI, 0.56–1.59; $P = .824$, M1b: SHR, 0.78; 95% CI, 0.29–2.12; $P = .629$, and M1c: SHR, 1.50; 95% CI, 0.75–3.02; $P = .251$). Compared with surgery, chemotherapy conferred a greater survival benefit across M1 subcategories (M1a: SHR, 0.65, 95% CI, 0.44–0.96; $P = .031$, M1b: SHR, 0.34; 95% CI, 0.16–0.74; $P = .006$, and M1c: SHR, 0.32; 95% CI, 0.16–0.64; $P = .001$).

Table 2. Multivariate Analysis of Cancer-Specific and All-Cause Mortality^a

	Training Set		Validation Set		Whole Set	
	SHR (95% CI)	P Value	SHR (95% CI)	P Value	SHR (95% CI)	P Value
Part I: cancer-specific mortality						
M1a	Ref		Ref		Ref	
M1b	1.48 (1.29–1.68)	<.001	1.32 (1.17–1.51)	<.001	1.39 (1.27–1.53)	<.001
M1c	2.45 (2.18–2.75)	<.001	2.15 (1.92–2.42)	<.001	2.29 (2.11–2.48)	<.001
Part II: all-cause mortality						
M1a	Ref		Ref		Ref	
M1b	1.47 (1.30–1.66)	<.001	1.35 (1.20–1.53)	<.001	1.41 (1.29–1.53)	<.001
M1c	2.38 (2.14–2.65)	<.001	2.09 (1.88–2.33)	<.001	2.22 (2.06–2.41)	<.001

Abbreviation: SHR, subdistribution hazard ratio.

^aAdjusted variables included age, race/ethnicity, marital status, histologic grade, AJCC T & N category, molecular subtype, and treatment modality. For detailed data, see supplemental eTables 5 and 6.

In addition, comparisons between lumpectomy and mastectomy are presented in supplemental eTable 10. No significant difference in mortality was observed.

Discussion

This study focused on the association between anatomic extent of metastatic disease and CSM in patients with de novo MBC. We found that involvement of liver and brain and of multiple metastatic sites were independently associated with CSM. We also further subdivided patients with significantly different prognoses into M1a, M1b, or M1c subcategories, and found that cumulative incidence rates of both CSM and all-cause mortality were significantly different across M1 subcategories. Our findings indicate that selected patients might benefit from aggressive locoregional treatment and that subdivision of M1 stage may guide individualized treatment planning.

Consistent with previous research,¹⁹ we found that brain and liver involvement were each independently associated with an unfavorable prognosis for patients with de novo MBC. In our study, the number of sites involved proved to be an independent predictor for CSM, which was accordant with the findings of many previous studies, which reported HRs ranging from 1.45 (95% CI, 1.35–1.55) to 1.56 (95% CI, 1.02–2.40).^{4,5,20,21} The results of both the previous study and the present study indicated that metastatic sites and the number of sites involved might be key parameters for risk stratification. In autopsy studies, patients with brain metastases were reported as more likely to have multiple sites involved.²² Interestingly, no significant difference in survival was observed between patients with single and multiple metastatic sites in the presence of brain involvement in our study. Hence, we established an M1 subdivision system and divided patients with bone-only or lung-only metastases into the M1a category due

Figure 2. Cumulative incidence curves of cancer-specific mortality stratified by treatment modality in patients with (A) M1a, (B) M1b, and (C) M1c disease in the whole set. Patients receiving no treatment were used as the reference category and data are presented as SHR (95% CI).

Abbreviations: BCSD, breast cancer-specific death; chemo, chemotherapy; SHR, subdistribution hazard ratio; surg, surgery.

Table 3. Association of Cancer-Specific Mortality With Treatment Modality^a

	Model 1		Model 2		Model 3	
	SHR (95% CI)	P Value	SHR (95% CI)	P Value	SHR (95% CI)	P Value
Part I: univariate analysis						
M1a						
None	Ref					
Surgery only	0.59 (0.50–0.69)	<.001	Ref			
Chemo only	0.80 (0.71–0.91)	<.001	1.36 (1.15–1.60)	<.001	Ref	
Surgery + chemo	0.45 (0.40–0.51)	<.001	0.77 (0.65–0.91)	.002	0.57 (0.49–0.65)	<.001
M1b						
None	Ref					
Surgery only	0.67 (0.51–0.89)	.006	Ref			
Chemo only	0.63 (0.53–0.76)	<.001	0.94 (0.71–1.24)	.649	Ref	
Surgery + chemo	0.52 (0.43–0.63)	<.001	0.77 (0.58–1.03)	.075	0.82 (0.67–1.00)	.048
M1c						
None	Ref					
Surgery only	0.68 (0.52–0.88)	.004	Ref			
Chemo only	0.55 (0.48–0.63)	<.001	0.81 (0.63–1.05)	.107	Ref	
Surgery + chemo	0.37 (0.31–0.44)	<.001	0.55 (0.41–0.72)	<.001	0.68 (0.58–0.79)	<.001
Part II: multivariate analysis						
M1a						
None	Ref					
Surgery only	0.57 (0.48–0.67)	<.001	Ref			
Chemo only	0.72 (0.62–0.83)	<.001	1.27 (1.06–1.51)	.008	Ref	
Surgery + chemo	0.39 (0.34–0.46)	<.001	0.66 (0.55–0.79)	<.001	0.55 (0.47–0.63)	<.001
M1b						
None	Ref					
Surgery only	0.62 (0.47–0.83)	.001	Ref			
Chemo only	0.54 (0.44–0.68)	<.001	0.87 (0.65–1.18)	.377	Ref	
Surgery + chemo	0.46 (0.36–0.58)	<.001	0.73 (0.54–1.00)	.048	0.84 (0.68–1.03)	.094
M1c						
None	Ref					
Surgery only	0.59 (0.44–0.80)	<.001	Ref			
Chemo only	0.53 (0.45–0.61)	<.001	0.89 (0.66–1.20)	0.438	Ref	
Surgery + chemo	0.32 (0.26–0.38)	<.001	0.54 (0.39–0.74)	<.001	0.60 (0.51–0.71)	<.001

Abbreviations: Chemo, chemotherapy; SHR, subdistribution hazard ratio.

^aIn both the univariate and multivariate analyses, a different treatment modality was selected as the reference category to perform the pairwise comparison ("no treatment" for Model 1, "surgery only" for Model 2, and "chemo only" for Model 3). The competing risk model was adjusted for age, race/ethnicity, marital status, histologic grade, AJCC T & N category, molecular subtype, and treatment modality (data not shown).

to relatively favorable prognosis. Those with brain involvement were categorized as M1c. In our study, patients with M1b disease had an approximately 40% increased mortality risk, and those with M1c disease exhibited greater than 2-fold higher risk of mortality compared with those with M1a disease. Similar directions of the association were observed across different molecular subtypes.

Palliative systemic therapy is usually considered the therapeutic backbone for patients with metastatic breast

cancer.^{12,14} Despite this, studies have reported that approximately 40% of women receive locoregional surgery and some patients desire a complete excision of primary tumor for psychosocial reasons,^{23–25} and many other reports reached an entirely different conclusion regarding primary tumor surgery versus systemic therapy. A Turkish study (MF07-01) reported a 34% higher overall survival for patients receiving locoregional surgery combined with chemotherapy compared with those receiving chemotherapy

alone (HR, 0.66; 95% CI, 0.49–0.88; $P=.005$), especially in those with more indolent disease, such as HoR+/HER2-subtype and single-bone involvement.¹⁵ Similarly, our data revealed that for patients with bone metastases (mainly classified as M1a), primary tumor surgery might provide a favorable prognosis. In addition, numerous retrospective studies and meta-analyses had reaffirmed the survival benefit associated with locoregional surgery with or without chemotherapy for advanced disease.^{23,24,26,27} On the contrary, an Indian trial reported a significant decrease in distant progression-free survival (HR, 1.42; 95% CI, 1.08–1.85; $P=.012$) in patients receiving locoregional treatment compared with chemotherapy only.²⁸ Cautious interpretation was suggested because of the insufficient use of subsequent systemic therapy and targeted anti-HER2 therapy. In addition, the lack of stratification factors might lead to unbalanced inclusion.

In our study, we attempted to account for margin status, which was not accessible in the SEER database, and divided the whole population into patients receiving no surgery, lumpectomy, or mastectomy. We hypothesized that patients undergoing mastectomy may be more likely to receive a negative margin, and thus surgery types might be an alternative indicator for margin status to some extent.²⁹ Many previous works reported no survival gain from surgery with positive margins in metastatic setting.^{25,30,31} However, our study presented no survival difference between women receiving mastectomy or lumpectomy, and therefore it could be speculated that many patients may obtain clear margins after lumpectomy. Similarly, Lane et al²⁵ reported a positive margin rate of <20% for patients receiving lumpectomy or mastectomy based on a national database. However, we cannot determine whether more aggressive surgery (simple of modified mastectomy) can provide additional benefits.

We also found that surgical resection did not improve survival for women with TNBC across M1 subcategories. Similarly, Neuman et al³² reported that survival gain was observed among women with ER/PR-positive and/or HER2-amplified disease, although not in those with TNBC, indicating that less benefit might be obtained from primary surgery of metastatic disease with aggressive tumor biology.

Our findings may have some implications for clinical practice. For patients with M1a disease, the combination of surgery and chemotherapy is preferred due to the approximately 50% reduction in mortality risk. It is reasonable to assume that these patients present better performance status and more favorable prognosis and that they can tolerate and benefit from the aggressive combination. For the M1b subcategory, which consists of patients with different metastatic burden, combined treatment has no clinical necessity because only statistically borderline survival improvement is observed

between monotherapies and combination therapy; both surgery alone and chemotherapy alone may benefit specific subgroups of patients. Further investigation is required. As for patients with M1c disease, systemic chemotherapy alone may be considered after considering the surgical difficulty, potential decline in quality of life, possible visceral crisis, and palliation of symptoms. Among women who did not receive RT, those receiving chemotherapy alone experienced a 30% (70% in those with TNBC) reduction in mortality risk compared with those receiving surgery only. The fact that the lowest SHRs were associated with combined therapy may be attributed to selection bias, and we believe that this bias increases with upstaging of the metastatic disease. Women with M1c disease tend to present with organ failure and short life expectancy²⁶; however, those receiving locoregional surgery may have better general well-being, thus leading to the lowest SHRs observed.

Despite the possible benefits from surgery, systemic therapy is still the preferred choice for MBC.^{12,14} In our study, the M1a subcategory contains more ER/PR-positive disease, which can be well-controlled by some state-of-the-art therapies, such as the combination of CDK4/6 inhibitors with endocrine therapies. Nonetheless, it is of great interest and necessity to study whether and when to perform primary tumor surgery for selected patients with long-term disease control by CDK4/6 inhibitors.

This work has several limitations. First, some variables were not available in SEER, such as the number and size of metastatic lesions and other metastatic sites. Therefore, involvement of contralateral axillary lymph nodes, pleura, and other sites was not included for further subdivision of M1 category. The variable “number of metastatic sites,” which was the total number of sites involved in the bone, brain, liver, or lung, might cause potential bias. Second, SEER did not provide detailed information on locoregional treatment, making it impossible to adjust for margin status, surgery of the axilla and metastatic disease, and use of RT. Neither could we account for the systemic therapy in terms of use, timing of initiation, and patient response, preventing adjustment for the sequence of surgery and systemic therapy and other potential confounders. Third, other confounders such as Charlson comorbidity score were not adjusted for, and the possibly unbalanced distribution of comorbidity might be another source of selection bias, resulting in the observed benefit from surgery. Finally, each M1 subcategory consists of a heterogeneous group of patients; therefore, the treatment advice based on M1 subcategory may not apply to each individual in that subcategory. We acknowledge that the M1 category subdivisions and the observed relationship between M1 subcategories and treatment modality should be prospectively validated. As treatment moves toward precision and personalization,

multigene assays and biologic subtypes in addition to cancer staging may also play an increasingly important role in clinical decision-making.

Conclusions

The subdivision of M1 category reported herein, taking into account the metastatic sites and number of sites involved, may provide both patients with de novo MBC and oncologists with critical information for informing prognosis and help facilitate treatment choice. Treatment offered to women with metastatic disease should be determined by a coordinated, multidisciplinary team. As the prolongation of survival resulted from systemic therapy, primary tumor surgery may further benefit selected patients who respond

well to systemic therapy. Although results of several related randomized trials are awaited, patients with de novo MBC should be provided with the currently available evidence when determining treatment approach.

Submitted November 3, 2018; accepted for publication June 18, 2019.

Author contributions: Study concept and design: Lin, Wu, Zhu. Data acquisition: Lin, Ding, Goh. Data analysis and interpretation: Lin, Wu, Ding, Andriani, Lu, Shen. Manuscript preparation: All authors. Final approval: Zhu.

Disclosures: The authors have disclosed that they have not received any financial considerations from any person or organization to support the preparation, analysis, results, or discussion of this article.

Correspondence: Li Zhu, MD, PhD, Comprehensive Breast Health Center, Ruijin Hospital, 197 Ruijin Er Road, Huangpu District, Shanghai 200025, China. Email: zhuli8@yeah.net

References

- DeSantis CE, Ma J, Goding Sauer A, et al. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin* 2017;67:439–448.
- Mariotto AB, Etzioni R, Hurlbert M, et al. Estimation of the number of women living with metastatic breast cancer in the United States. *Cancer Epidemiol Biomarkers Prev* 2017;26:809–815.
- Largillier R, Ferrero JM, Doyen J, et al. Prognostic factors in 1,038 women with metastatic breast cancer. *Ann Oncol* 2008;19:2012–2019.
- Hölzel D, Eckel R, Bauerfeind I, et al. Survival of de novo stage IV breast cancer patients over three decades. *J Cancer Res Clin Oncol* 2017;143:509–519.
- Andre F, Slimane K, Bachelot T, et al. Breast cancer with synchronous metastases: trends in survival during a 14-year period. *J Clin Oncol* 2004;22:3302–3308.
- Lobbzoo DJ, van Kampen RJ, Voogd AC, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? *Br J Cancer* 2015;112:1445–1451.
- Amin MB, Edge SB, Greene FL, et al. *AJCC Cancer Staging Manual*, 8th ed. New York, NY: Springer; 2017.
- Brierley JD, Gospodarowicz MK, Wittekind C, et al. *TNM classification of malignant tumours*, 8th ed. Oxford, UK: Wiley Blackwell; 2017.
- 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.
- Zou X, You R, Liu H, et al. Establishment and validation of M1 stage subdivisions for de novo metastatic nasopharyngeal carcinoma to better predict prognosis and guide treatment. *Eur J Cancer* 2017;77(Supplement C):117–126.
- Shen L, Li W, Wang S, et al. Image-based multilevel subdivision of M1 category in TNM Staging System for metastatic nasopharyngeal carcinoma. *Radiology* 2016;280:805–814.
- Harbeck N, Gnant M. Breast cancer. *Lancet* 2017;389:1134–1150.
- Gradishar WJ, Anderson BO, Aft R, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 1.2018. To view the most recent version, visit NCCN.org. Accessed March 20, 2018.
- Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol* 2017;28:16–33.
- Soran A, Ozmen V, Ozbaz S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. *Ann Surg Oncol* 2018;25:3141–3149.
- Surveillance, Epidemiology, and End Results Program. SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2017 Sub (1973-2015) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program. Based on November 2017 submission. Released April 2018.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141–1154.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA* 2019;321:288–300.
- Rahman ZU, Frye DK, Smith TL, et al. Results and long term follow-up for 1581 patients with metastatic breast carcinoma treated with standard dose doxorubicin-containing chemotherapy: a reference. *Cancer* 1999;85:104–111.
- Yamamura J, Kamigaki S, Fujita J, et al. The difference in prognostic outcomes between De Novo stage IV and recurrent metastatic patients with hormone receptor-positive, HER2-negative breast cancer. *In Vivo* 2018;32:353–358.
- Cummings MC, Simpson PT, Reid LE, et al. Metastatic progression of breast cancer: insights from 50 years of autopsies. *J Pathol* 2014;232:23–31.
- Thomas A, Khan SA, Chrischilles EA, et al. Initial surgery and survival in stage IV breast cancer in the United States, 1988-2011. *JAMA Surg* 2016;151:424–431.
- Warschaw R, Güller U, Tarantino I, et al. Improved survival after primary tumor surgery in metastatic breast cancer: a propensity-adjusted, population-based SEER trend analysis. *Ann Surg* 2016;263:1188–1198.
- Lane WO, Thomas SM, Blitzblau RC, et al. Surgical resection of the primary tumor in women with de novo stage IV breast cancer: contemporary practice patterns and survival analysis. *Ann Surg* 2019;269:537–544.
- Lu S, Wu J, Fang Y, et al. The impact of surgical excision of the primary tumor in stage IV breast cancer on survival: a meta-analysis. *Oncotarget* 2017;9:11816–11823.
- Petrelli F, Barni S. Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. *Med Oncol* 2012;29:3282–3290.
- Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol* 2015;16:1380–1388.
- Ruiterkamp J, Ernst MF, van de Poll-Franse LV, et al. Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. *Eur J Surg Oncol* 2009;35:1146–1151.
- Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery* 2002;132:620–626; discussion 626–627.
- Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* 2006;24:2743–2749.
- Neuman HB, Morrogh M, Gonen M, et al. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer* 2010;116:1226–1233.

See JNCCN.org for supplemental online content.

Supplemental online content for:

Subdivision of M1 Stage for De Novo Metastatic Breast Cancer to Better Predict Prognosis and Response to Primary Tumor Surgery

Caijin Lin, M.Med; Jiayi Wu, MD; Shuning Ding, M.Med; Chihwan Goh, M.Med; Lisa Andriani, M.Med; Shuangshuang Lu, MD; Kunwei Shen, MD, PhD; and Li Zhu, MD, PhD

J Natl Compr Canc Netw 2019;17(12):1521–1528

eFigure 1: Cumulative Incidence Curves of Cancer-Specific Mortality Stratified by Site

eFigure 2: Cumulative Incidence Curves of Cancer-Specific Mortality and All-Cause Mortality

eFigure 3: Cumulative Incidence Curves of Cancer-Specific Mortality Stratified by Treatment Modality

eTable 1: Detailed Baseline Characteristics

eTable 2: Baseline Characteristics Stratified by M1 Subcategory

eTable 3: Univariate and Multivariate Analysis of Cancer-Specific Mortality in the Training Set: A Competing Risk Regression Model

eTable 4: Description of Different Patient Groups Based on Independent Prognostic Factors

eTable 5: Multivariate Analysis of Cancer-Specific Mortality: A Competing Risk Model

eTable 6: Multivariate Analysis of All-Cause Mortality: Cox Proportional Hazards Model

eTable 7: Baseline Patient Characteristics by Molecular Subtype

eTable 8: Median Survival by M1 Subcategory, Stratified by Molecular Subtype and Histologic Grade

eTable 9: Multivariate Analysis of Cancer-Specific Mortality by Treatment Modality

eTable 10: Association of Primary Tumor Surgery With Mortality

eAppendix 1: Validation of M1 Category Subdivision System

eFigure 1. Cumulative incidence curves of cancer-specific mortality stratified by single/multiple sites involved in the (A–C) absence or (D–F) presence of brain involvement in the (A, D) training, (B, E) validation, and (C, F) whole sets. Abbreviation: BCSD, breast cancer–specific death.

Figure 2. Cumulative incidence curves of (A–D) cancer-specific and (E–H) all-cause mortality stratified by M1 subcategories in patients with (A, E) HoR+/HER2–, (B, F) HoR+/HER2+, (C, G) HoR–/HER2+, or (D, H) triple-negative breast cancer in the whole set. *P* values were estimated and compared based on Gray’s test (A–D) or log-rank test (E–H).

Abbreviations: BCSD, breast cancer–specific death; HoR, hormone receptor; LG, log-rank.

eFigure 3. Cumulative incidence curves of cancer-specific mortality stratified by treatment modality across (A, D) M1a, (B, E) M1b, and (C, F) M1c in patients not receiving RT (A–C) and those with TNBC not receiving RT (D–F). Patients receiving no treatment were used as the reference category and data are presented as SHR (95% CI).

Abbreviations: BCSD, breast cancer-specific death; chemo, chemotherapy; RT, radiotherapy; SHR, subdistribution hazard ratio; surg, surgery.

eTable 1. Detailed Baseline Patient Characteristics (N=8,582)

	Training Set n (%)	Validation Set n (%)	P Value
Sex			.668
Female	4,245 (98.9)	4,249 (99.0)	
Male	46 (1.1)	42 (1.0)	
Race/Ethnicity			.632
White	2,765 (64.4)	2,755 (64.2)	
Black	712 (16.6)	720 (16.8)	
Hispanic	503 (11.7)	476 (11.1)	
Asian	294 (6.9)	317 (7.4)	
Other	17 (0.4)	23 (0.5)	
Year of diagnosis			.394
2010	749 (17.5)	810 (18.9)	
2011	858 (20.0)	820 (19.1)	
2012	864 (20.1)	828 (19.3)	
2013	920 (21.4)	921 (21.5)	
2014	900 (21.0)	912 (21.3)	
ER status			.029
Negative	1,040 (24.2)	1,128 (26.3)	
Positive	3,251 (75.8)	3,163 (73.7)	
PR status			.021
Negative	1,614 (37.6)	1,718 (40.0)	
Positive	2,677 (62.4)	2,573 (60.0)	
HER2 status			.827
Negative	3,129 (72.9)	3,138 (73.1)	
Positive	1,162 (27.1)	1,153 (26.9)	
Median all-cause mortality by molecular subtype (95% CI), mo ^a			
HoR+/HER2-	33.0 (30.7-35.3)	33.0 (30.7-35.3)	.609
HoR+/HER2+	42.0 (34.9-49.1)	44.0 (37.4-50.6)	.337
HoR-/HER2+	33.0 (25.7-40.3)	29.0 (24.0-34.0)	.236
Triple-negative	12.0 (10.7-13.3)	12.0 (11.0-13.0)	.868
Median cancer-specific mortality by molecular subtype (95% CI), mo ^b			
HoR+/HER2-	37.0 (34.1-39.9)	38.0 (34.7-41.3)	.628
HoR+/HER2+	47.0 (41.0-NR)	46.0 (40.3-51.7)	.237
HoR-/HER2+	40.0 (30.3-39.7)	33.0 (27.0-39.0)	.159
Triple-negative	12.0 (10.6-13.4)	13.0 (12.0-14.0)	.784

Abbreviations: ER, estrogen receptor; HoR, hormone receptor; NR, not reached; PR, progesterone receptor.

^aP values estimated and compared using log-rank test.

^bP values estimated and compared using Gray's test.

eTable 2. Baseline Characteristics Stratified by M1 Subcategory

	Training Set				Validation Set				Whole Set			
	M1a n (%)	M1b n (%)	M1c n (%)	P Value	M1a n (%)	M1b n (%)	M1c n (%)	P Value	M1a n (%)	M1b n (%)	M1c n (%)	P Value
Total	2,441	787	1,063		2,448	815	1,028		4,889	1,602	2,091	
Age, y				.020				.003				<.001
<40	218 (8.9)	92 (11.7)	113 (10.6)		207 (8.5)	70 (8.6)	99 (9.6)		425 (8.7)	162 (10.1)	212 (1.1)	
41–60	1,013 (41.5)	338 (42.9)	485 (45.6)		1,022 (41.7)	342 (42.0)	486 (47.3)		2,035 (41.6)	680 (42.4)	971 (46.4)	
61–80	986 (40.4)	290 (36.8)	386 (36.3)		980 (40.0)	338 (41.5)	377 (36.7)		1,966 (40.2)	628 (39.2)	763 (36.5)	
>81	224 (9.2)	67 (8.5)	79 (7.4)		239 (9.8)	65 (8.0)	66 (6.4)		463 (9.5)	132 (8.2)	145 (6.9)	
Sex				.462				.045				.071
Female	2,414 (98.9)	779 (99.0)	1,056 (99.3)		2,424 (99.0)	800 (98.2)	1,021 (99.3)		4,838 (99.0)	1,579 (98.6)	2,077 (99.3)	
Male	27 (1.1)	8 (1.0)	7 (0.7)		24 (1.0)	15 (1.8)	7 (0.7)		51 (1.0)	23 (1.4)	14 (0.7)	
Race/Ethnicity				.143				.557				.163
White	1,582 (64.8)	497 (63.2)	676 (63.6)		1,595 (65.2)	523 (64.2)	647 (62.9)		3,177 (65.0)	1,020 (63.7)	1,323 (63.3)	
Black	391 (16.0)	136 (17.3)	193 (18.2)		410 (16.7)	127 (15.6)	175 (17.0)		801 (16.4)	263 (16.4)	368 (17.6)	
Hispanic	291 (11.9)	76 (9.7)	109 (10.3)		280 (11.4)	99 (12.1)	124 (12.1)		571 (11.7)	175 (10.9)	233 (11.1)	
Asian	165 (6.8)	74 (9.4)	78 (7.3)		151 (6.2)	64 (7.9)	79 (7.7)		316 (6.5)	138 (8.6)	157 (7.5)	
Other	12 (0.5)	4 (0.5)	7 (0.7)		12 (0.5)	2 (0.2)	3 (0.3)		24 (0.5)	6 (0.4)	10 (0.5)	
Marital status				.372				.700				.281
Unmarried	1,307 (53.5)	416 (52.9)	593 (55.8)		1,313 (53.6)	435 (53.4)	566 (55.1)		2,620 (53.6)	851 (53.1)	1,159 (55.4)	
Married	1,134 (46.5)	371 (47.1)	470 (44.2)		1,135 (46.4)	380 (46.6)	462 (44.9)		2,269 (46.4)	751 (46.9)	932 (44.6)	
Year of diagnosis				.246				.277				.774
2010	476 (19.5)	149 (18.9)	185 (17.4)		429 (17.5)	153 (18.8)	167 (16.2)		905 (18.5)	302 (18.9)	352 (16.8)	
2011	460 (18.8)	145 (18.4)	215 (20.2)		485 (19.8)	175 (21.5)	198 (19.3)		945 (19.3)	320 (20.0)	413 (19.8)	
2012	456 (18.7)	168 (21.3)	204 (19.2)		505 (20.6)	140 (17.2)	219 (21.3)		961 (19.7)	308 (19.2)	423 (20.2)	
2013	504 (20.6)	176 (22.4)	241 (22.7)		534 (21.8)	174 (21.3)	212 (20.6)		1038 (21.2)	350 (21.8)	453 (21.7)	
2014	545 (22.3)	149 (18.9)	218 (20.5)		495 (20.2)	173 (21.2)	232 (22.6)		1040 (21.3)	322 (20.1)	450 (21.5)	
Histologic grade				<.001				<.001				<.001
Well-differentiated	230 (9.4)	45 (5.7)	47 (4.4)		204 (8.3)	44 (5.4)	58 (5.6)		434 (8.9)	89 (5.6)	105 (5.0)	
Moderately differentiated	1,036 (42.4)	338 (42.9)	397 (37.3)		1,088 (44.4)	331 (40.6)	384 (37.4)		2,124 (43.4)	669 (41.8)	781 (37.4)	
Poorly differentiated	1,161 (47.6)	402 (51.1)	607 (57.1)		1,135 (46.4)	428 (52.5)	572 (55.6)		2,296 (47.0)	830 (51.8)	1,179 (56.4)	
Undifferentiated	14 (0.6)	2 (0.3)	12 (1.1)		21 (0.9)	12 (1.5)	14 (1.4)		35 (0.7)	14 (0.9)	26 (1.2)	

Abbreviations: Chemo, chemotherapy; ER, estrogen receptor; HoR, hormone receptor; PR, progesterone receptor.

(continued on next page)

Table 2. Baseline Characteristics Stratified by M1 Subcategory (cont.)

	Training Set				Validation Set				Whole Set			
	M1a n (%)	M1b n (%)	M1c n (%)	P Value	M1a n (%)	M1b n (%)	M1c n (%)	P Value	M1a n (%)	M1b n (%)	M1c n (%)	P Value
AJCC T stage				<.001				<.001				<.001
T0	188 (7.7)	72 (9.1)	117 (11.0)		200 (8.2)	75 (9.2)	110 (10.7)		388 (7.9)	147 (9.2)	227 (10.9)	
T1	269 (11.0)	81 (10.3)	105 (9.9)		284 (11.6)	84 (10.3)	89 (8.7)		553 (11.3)	165 (10.3)	194 (9.3)	
T2	806 (33.0)	243 (30.9)	277 (26.1)		798 (32.6)	234 (28.7)	277 (26.9)		1,604 (32.8)	477 (29.8)	554 (26.5)	
T3	426 (17.5)	116 (14.7)	161 (15.1)		430 (17.6)	140 (17.2)	150 (14.6)		856 (17.5)	256 (16.0)	311 (14.9)	
T4	752 (30.8)	275 (34.9)	403 (37.9)		736 (30.1)	282 (34.6)	402 (39.1)		1,488 (30.4)	557 (34.8)	805 (38.5)	
AJCC N stage				<.001				.013				<.001
N0	637 (26.1)	204 (25.9)	314 (29.5)		662 (27.0)	206 (25.3)	290 (28.2)		1,299 (26.6)	410 (25.6)	604 (28.9)	
N1	1,028 (42.1)	378 (48.0)	486 (45.7)		1,063 (43.4)	392 (48.1)	472 (45.9)		2,091 (42.8)	770 (48.1)	958 (45.8)	
N2	329 (13.5)	107 (13.6)	116 (10.9)		286 (11.7)	101 (12.4)	128 (12.5)		615 (12.6)	208 (13.0)	244 (11.7)	
N3	447 (18.3)	98 (12.5)	147 (13.8)		437 (17.9)	116 (14.2)	138 (13.4)		884 (18.1)	214 (13.4)	285 (13.6)	
ER status				<.001				<.001				<.001
Negative	538 (22.0)	227 (28.8)	363 (34.1)		496 (20.3)	218 (26.7)	326 (31.7)		1,034 (21.1)	445 (27.8)	689 (32.9)	
Positive	1,903 (78.0)	560 (71.2)	700 (65.9)		1,952 (79.7)	597 (73.3)	702 (68.3)		3,855 (78.9)	1,157 (72.2)	1,402 (67.0)	
PR status				<.001				<.001				<.001
Negative	856 (35.1)	331 (42.1)	531 (50.0)		804 (32.8)	324 (39.8)	486 (47.3)		1,660 (34.0)	655 (40.9)	1,017 (48.6)	
Positive	1,585 (64.9)	456 (57.9)	532 (50.0)		1,644 (67.2)	491 (60.2)	542 (52.7)		3,229 (66.0)	947 (59.1)	1,074 (51.4)	
HER2 status				<.001				<.001				<.001
Negative	1,926 (78.9)	548 (69.6)	664 (62.5)		1,912 (78.1)	553 (67.9)	664 (64.6)		3,838 (78.5)	1,101 (68.7)	1,328 (63.5)	
Positive	515 (21.1)	239 (30.4)	399 (37.5)		536 (21.9)	262 (32.1)	364 (35.4)		1,051 (21.5)	501 (31.3)	763 (36.5)	
Molecular subtype				<.001				<.001				<.001
HoR+/HER2-	1,583 (64.9)	434 (55.1)	474 (44.6)		1,601 (65.4)	457 (56.1)	496 (48.2)		3,184 (65.1)	891 (55.6)	970 (46.4)	
HoR+/HER2+	354 (14.5)	140 (17.8)	250 (23.5)		390 (15.9)	154 (18.9)	231 (22.5)		744 (15.2)	294 (18.4)	481 (23.0)	
HoR-/HER2+	161 (6.6)	99 (12.6)	149 (14.0)		146 (6.0)	108 (13.3)	133 (12.9)		307 (6.3)	207 (12.9)	282 (13.5)	
Triple-negative	343 (14.1)	114 (14.5)	190 (17.9)		311 (12.7)	96 (11.8)	168 (16.3)		654 (13.4)	210 (13.1)	358 (17.1)	
Treatment				<.001				<.001				<.001
None	750 (30.6)	266 (32.6)	310 (30.2)		776 (31.8)	239 (30.4)	330 (31.0)		1,526 (31.2)	505 (31.5)	640 (30.6)	
Surgery only	347 (14.2)	79 (9.7)	59 (5.7)		338 (13.8)	70 (8.9)	61 (5.7)		685 (14.0)	149 (9.3)	120 (5.7)	
Chemo only	619 (25.3)	271 (33.3)	486 (47.3)		614 (25.2)	285 (36.2)	498 (46.8)		1,233 (25.2)	556 (34.7)	984 (47.1)	
Surgery and chemo only	732 (29.9)	199 (24.4)	173 (16.8)		713 (29.2)	193 (24.5)	174 (16.4)		1,445 (29.6)	392 (24.5)	347 (16.6)	

Abbreviations: Chemo, chemotherapy; ER, estrogen receptor; HoR, hormone receptor; PR, progesterone receptor.

eTable 3. Univariate and Multivariate Analysis of Cancer-Specific Mortality in the Training Set: A Competing Risk Regression Model

	Univariate Analysis		Multivariate Analysis	
	SHR (95% CI)	P Value	SHR (95% CI)	P Value
Age, y				
<40	Ref		Ref	
41–60	1.38 (1.15–1.65)	.001	1.35 (1.12–1.62)	.002
61–80	1.69 (1.42–2.03)	<.001	1.56 (1.29–1.89)	<.001
>81	2.30 (1.84–2.87)	<.001	1.95 (1.54–2.46)	<.001
Sex				
Female	Ref		—	—
Male	0.85 (0.51–1.44)	.547	—	—
Race/Ethnicity				
White	Ref		Ref	
Black	1.31 (1.17–1.47)	<.001	1.18 (1.03–1.34)	.016
Hispanic	0.88 (0.76–1.02)	.094	1.02 (0.86–1.20)	.845
Asian	0.83 (0.68–1.01)	.059	0.89 (0.72–1.09)	.268
Other	0.62 (0.29–1.32)	.215	0.52 (0.19–1.42)	.203
Marital status				
Unmarried	Ref		Ref	
Married	0.75 (0.69–0.83)	<.001	0.88 (0.79–0.98)	.015
Histologic grade				
Well-differentiated	Ref		Ref	
Moderately differentiated	1.27 (1.03–1.55)	.024	1.25 (1.01–1.55)	.042
Poorly differentiated	1.89 (1.55–2.31)	<.001	1.73 (1.39–2.14)	<.001
Undifferentiated	1.82 (0.99–3.33)	.054	1.61 (0.94–2.75)	.081
AJCC T stage				
T0	Ref		Ref	—
T1	0.32 (0.12–0.85)	.022	0.37 (0.19–0.71)	.003
T2	0.31 (0.12–0.81)	.017	0.37 (0.19–0.70)	.002
T3	0.34 (0.13–0.90)	.030	0.41 (0.21–0.78)	.007
T4	0.46 (0.18–1.23)	.121	0.50 (0.26–0.95)	.035
AJCC N stage				
N0	Ref		Ref	
N1	0.87 (0.77–0.99)	.033	0.84 (0.74–0.96)	.010
N2	0.82 (0.70–0.96)	.017	0.88 (0.74–1.04)	.123
N3	0.79 (0.67–0.92)	.003	0.81 (0.69–0.96)	.014
Molecular subtype				
HoR+/HER2–	Ref		Ref	
HoR+/HER2+	0.79 (0.68–0.91)	.001	0.76 (0.65–0.89)	<.001
HoR–/HER2+	1.06 (0.89–1.26)	.517	0.94 (0.78–1.14)	.533
Triple-negative	2.62 (2.34–2.94)	<.001	2.42 (2.10–2.79)	<.001
Bone involvement				
No	Ref		—	—
Yes	0.92 (0.84–1.02)	.124	—	—

(continued on next page)

Abbreviations: Chemo, chemotherapy; ER, estrogen receptor; HoR, hormone receptor; PR, progesterone receptor.

eTable 3. Univariate and Multivariate Analysis of Cancer-Specific Mortality in the Training Set: A Competing Risk Regression Model (cont.)

	Univariate Analysis		Multivariate Analysis	
	SHR (95% CI)	P Value	SHR (95% CI)	P Value
Brain involvement				
No	Ref		Ref	
Yes	2.51 (2.16–2.92)	<.001	2.13 (1.80–2.52)	<.001
Liver involvement				
No	Ref		Ref	
Yes	1.79 (1.62–1.98)	<.001	1.71 (1.51–1.95)	<.001
Lung involvement				
No	Ref		Ref	
Yes	1.57 (1.43–1.73)	<.001	1.14 (1.00–1.28)	.043
Number of metastatic sites				
Binary classifications 1				
1 site	Ref	—	Ref	
>1 site	1.89 (1.72–2.07)	<.001	1.28 (1.11–1.47)	<.001
Binary classifications 2				
1 or 2 sites	Ref		Ref	
>2 sites	2.33 (2.03–2.69)	<.001	1.11 (0.91–1.35)	.318
Treatment modality				
None	Ref		Ref	
Surgery only	0.63 (0.53–0.74)	<.001	0.67 (0.56–0.80)	<.001
Chemo only	0.74 (0.66–0.82)	<.001	0.59 (0.52–0.68)	<.001
Surgery and chemo	0.48 (0.42–0.54)	<.001	0.44 (0.38–0.52)	<.001

Abbreviations: Chemo, chemotherapy; ER, estrogen receptor; HoR, hormone receptor; PR, progesterone receptor.

eTable 4. Description of Different Patient Groups Based on Independent Prognostic Factors

Brain Involvement	Liver Involvement	Multiple Sites Involvement	Group	M1 Subcategory	SHR (95% CI)	P value
Yes	Yes	Yes	A ^a	M1c	—	—
Yes	No	Yes				
Yes	No	No			Group A vs B 1.23 (1.03–1.46)	.022
No	Yes	Yes	B ^b	M1c		
No	Yes	No	C ^c	M1b	Group B vs C 1.61 (1.33–1.94)	<.001
No	No	Yes	D ^d	M1b	Group C vs D 1.02 (0.83–1.26)	.832
No	No	No	E ^e	M1a	Group D vs E 1.40 (1.19–1.64)	<.001
					—	—

Abbreviation: SHR, subdistribution hazard ratio.

^aInvolvement of brain, irrespective of number of metastatic sites.

^bInvolvement of liver and multiple sites except brain.

^cLiver involvement only.

^dInvolvement of multiple sites except brain or liver.

^eInvolvement of single site except brain or liver.

eTable 5. Multivariate Analysis of Cancer-Specific Mortality: A Competing Risk Model

	Training Set		Validation Set		Whole Set	
	SHR (95% CI)	P Value	SHR (95% CI)	P Value	SHR (95% CI)	P Value
M1 subdivision						
M1a	Ref		Ref		Ref	
M1b	1.48 (1.29–1.68)	<.001	1.32 (1.17–1.51)	<.001	1.39 (1.27–1.53)	<.001
M1c	2.45 (2.18–2.75)	<.001	2.15 (1.92–2.42)	<.001	2.29 (2.11–2.48)	<.001
Age, y						
<40	Ref		Ref		Ref	
41–60	1.33 (1.10–1.60)	.002	1.38 (1.14–1.69)	.001	1.38 (1.21–1.58)	<.001
61–80	1.56 (1.29–1.90)	<.001	1.57 (1.30–1.97)	<.001	1.61 (1.40–1.85)	<.001
>81	1.92 (1.52–2.43)	<.001	1.69 (1.33–2.25)	<.001	1.84 (1.54–2.20)	<.001
Race/Ethnicity						
White	Ref		—	—	Ref	
Black	1.17 (1.03–1.33)	.020	—	—	1.14 (1.04–1.25)	.005
Hispanic	1.02 (0.86–1.20)	.846	—	—	1.00 (0.89–1.12)	.983
Asian	0.91 (0.74–1.11)	.338	—	—	1.00 (0.87–1.15)	.982
Other	0.57 (0.21–1.51)	.256	—	—	0.79 (0.44–1.40)	.417
Marital status						
Unmarried	Ref		Ref		Ref	
Married	0.89 (0.81–0.99)	.026	0.83 (0.76–0.93)	<.001	0.86 (0.80–0.93)	<.001
Histologic grade						
Well-differentiated	Ref		Ref		Ref	
Moderately differentiated	1.30 (1.05–1.61)	.018	1.48 (1.16–1.87)	.001	1.39 (1.18–1.63)	<.001
Poorly differentiated	1.84 (1.48–2.29)	<.001	1.88 (1.47–2.39)	<.001	1.87 (1.59–2.20)	<.001
Undifferentiated	1.79 (1.05–3.04)	.033	1.70 (1.08–2.68)	.024	1.73 (1.21–2.46)	.002
AJCC T stage						
T0	Ref		Ref		Ref	
T1	0.42 (0.21–0.85)	.016	0.53 (0.24–1.30)	.131	0.50 (0.28–0.88)	.017
T2	0.43 (0.22–0.85)	.015	0.55 (0.25–1.31)	.136	0.51 (0.29–0.88)	.016
T3	0.46 (0.23–0.91)	.025	0.63 (0.29–1.52)	.259	0.55 (0.32–0.97)	.038
T4	0.56 (0.29–1.10)	.093	0.72 (0.33–1.73)	.421	0.66 (0.38–1.15)	.140
AJCC N stage						
N0	Ref		Ref		—	—
N1	0.83 (0.73–0.95)	.006	1.04 (0.90–1.18)	.611	—	—
N2	0.94 (0.79–1.11)	.453	0.94 (0.77–1.12)	.543	—	—
N3	0.85 (0.72–1.00)	.054	1.17 (0.99–1.37)	.053	—	—
Molecular subtype						
HoR+/HER2–	Ref		Ref		Ref	
HoR+/HER2+	0.76 (0.65–0.90)	<.001	0.95 (0.82–1.11)	.503	0.85 (0.76–0.95)	.003
HoR–/HER2+	0.98 (0.81–1.19)	.847	1.27 (1.06–1.53)	.011	1.11 (0.97–1.27)	.116
Triple-negative	2.63 (2.30–3.02)	<.001	2.81 (2.42–3.25)	<.001	2.70 (2.44–2.98)	<.001

(continued on next page)

Abbreviations: Chemo, chemotherapy; HoR, hormone receptor; SHR, subdistribution hazard ratio.

eTable 5. Multivariate Analysis of Cancer-Specific Mortality: A Competing Risk Model (cont.)						
	Training Set		Validation Set		Whole Set	
	SHR (95% CI)	P Value	SHR (95% CI)	P Value	SHR (95% CI)	P Value
Treatment modality						
None	Ref		Ref		Ref	
Surgery only	0.66 (0.55–0.79)	<.001	0.52 (0.44–0.63)	<.001	0.59 (0.52–0.68)	<.001
Chemo only	0.59 (0.52–0.68)	<.001	0.60 (0.53–0.69)	<.001	0.60 (0.54–0.66)	<.001
Surgery and chemo	0.44 (0.38–0.51)	<.001	0.32 (0.28–0.38)	<.001	0.38 (0.35–0.43)	<.001

Abbreviations: Chemo, chemotherapy; HoR, hormone receptor; SHR, subdistribution hazard ratio.

eTable 6. Multivariate Analysis of All-Cause Mortality: Cox Proportional Hazards Model

	Training Set		Validation Set		Whole Set	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
M1 subdivision						
M1a	Ref		Ref		Ref	
M1b	1.47 (1.30–1.66)	<.001	1.35 (1.20–1.53)	<.001	1.41 (1.29–1.53)	<.001
M1c	2.38 (2.14–2.65)	<.001	2.09 (1.88–2.33)	<.001	2.22 (2.06–2.41)	<.001
Age, y						
<40	Ref		Ref		Ref	
41–60	1.33 (1.10–1.60)	.003	1.32 (1.08–1.62)	.002	1.34 (1.17–1.54)	<.001
61–80	1.71 (1.41–2.07)	<.001	1.64 (1.34–2.01)	<.001	1.71 (1.49–1.96)	<.001
>81	2.38 (1.90–2.98)	<.001	2.25 (1.78–2.84)	<.001	2.33 (1.98–2.74)	<.001
Race/Ethnicity						
White	Ref		—	—	Ref	
Black	1.23 (1.09–1.39)	.001	—	—	1.19 (1.09–1.3)	<.001
Hispanic	1.09 (0.93–1.27)	.279	—	—	1.05 (0.94–1.16)	.410
Asian	0.98 (0.82–1.19)	.861	—	—	1.06 (0.93–1.2)	.407
Other	0.49 (0.22–1.09)	.080	—	—	0.83 (0.52–1.35)	.455
Marital status						
Unmarried	Ref		Ref		Ref	
Married	0.86 (0.78–0.95)	.002	0.82 (0.74–0.90)	.026	0.84 (0.79–0.9)	<.001
Histologic grade						
Well-differentiated	Ref		Ref		Ref	
Moderate differentiated	1.29 (1.05–1.57)	.014	1.32 (1.07–1.63)	.018	1.31 (1.13–1.51)	<.001
Poorly differentiated	1.86 (1.52–2.28)	<.001	1.71 (1.38–2.11)	<.001	1.78 (1.54–2.06)	<.001
Undifferentiated	1.86 (1.08–3.22)	.026	1.47 (0.96–2.24)	.033	1.64 (1.18–2.29)	.004
AJCC T stage						
T0	Ref		Ref		Ref	
T1	0.47 (0.21–1.07)	.073	0.67 (0.29–1.51)	.016	0.59 (0.33–1.05)	.073
T2	0.50 (0.22–1.13)	.095	0.64 (0.29–1.44)	.015	0.60 (0.34–1.06)	.078
T3	0.51 (0.23–1.16)	.109	0.75 (0.33–1.68)	.025	0.64 (0.36–1.14)	.127
T4	0.66 (0.30–1.48)	.314	0.87 (0.39–1.95)	.093	0.79 (0.45–1.39)	.411
AJCC N stage						
N0	Ref		—	—	Ref	
N1	0.81 (0.72–0.91)	<.001	—	—	0.89 (0.82–0.97)	.010
N2	0.94 (0.79–1.11)	.437	—	—	0.94 (0.83–1.05)	.274
N3	0.79 (0.67–0.93)	.004	—	—	0.95 (0.85–1.06)	.358
Molecular subtype						
HoR+/HER2–	Ref		Ref		Ref	
HoR+/HER2+	0.79 (0.68–0.91)	.001	0.94 (0.82–1.09)	<.001	0.86 (0.78–0.95)	.003
HoR–/HER2+	1.08 (0.90–1.28)	.412	1.35 (1.13–1.60)	.847	1.20 (1.06–1.35)	.004
Triple-negative	2.79 (2.46–3.17)	<.001	3.16 (2.76–3.62)	<.001	2.91 (2.66–3.19)	<.001
Treatment modality						
None	Ref		Ref		Ref	
Surgery only	0.67 (0.57–0.78)	<.001	0.48 (0.41–0.56)	<.001	0.57 (0.51–0.64)	<.001
Chemo only	0.55 (0.49–0.62)	<.001	0.58 (0.52–0.66)	<.001	0.57 (0.53–0.62)	<.001
Surgery and chemo	0.38 (0.33–0.44)	<.001	0.29 (0.25–0.34)	<.001	0.34 (0.30–0.37)	<.001

Abbreviations: chemo, chemotherapy; HoR, hormone receptor; HR, hazard ratio.

eTable 7. Baseline Patient Characteristics by Molecular Subtype

	HoR+/HER2- n (%)	HoR+/HER2+ n (%)	HoR-/HER2+ n (%)	TNBC n (%)
Total, n	5,045	1,519	796	1,222
M1 subdivisions				
M1a	3,184 (63.1)	744 (49.0)	307 (38.6)	654 (53.5)
M1b	891 (17.7)	481 (31.7)	207 (26.0)	210 (17.2)
M1c	970 (19.2)	481 (31.7)	282 (35.4)	358 (29.3)
Age, y				
<40	382 (7.6)	208 (13.7)	96 (12.1)	113 (9.2)
41–60	2,054 (40.7)	695 (45.8)	398 (50.0)	539 (44.1)
61–80	2,099 (41.6)	524 (34.5)	262 (32.9)	472 (38.6)
>81	510 (10.1)	92 (6.1)	40 (5.0)	98 (8.0)
Sex				
Female	4,986 (98.8)	1,500 (98.7)	795 (99.9)	1,213 (99.3)
Male	59 (1.2)	19 (1.3)	1 (0.1)	9 (0.7)
Race/Ethnicity				
White	3,380 (67.0)	962 (63.3)	478 (60.1)	700 (57.3)
Black	738 (14.6)	256 (16.9)	124 (15.6)	314 (25.7)
Hispanic	545 (10.8)	191 (12.6)	106 (13.3)	137 (11.2)
Asian	360 (7.1)	103 (6.8)	86 (10.8)	62 (5.1)
Other	22 (0.4)	7 (0.5)	2 (0.3)	9 (0.7)
Marital status				
Unmarried	2,731 (54.1)	807 (53.1)	406 (51.0)	686 (56.1)
Married	2,314 (45.9)	712 (46.9)	390 (49.0)	536 (43.9)
Histologic grade				
Well-differentiated	573 (11.4)	36 (2.4)	4 (0.5)	15 (1.2)
Moderately differentiated	2,576 (51.1)	585 (38.5)	208 (26.1)	205 (16.8)
Poorly differentiated	1,867 (37.0)	886 (58.3)	574 (72.1)	978 (80.0)
Undifferentiated	29 (0.6)	12 (0.8)	10 (1.3)	24 (2.0)
AJCC T stage				
T0	485 (9.6)	133 (8.8)	66 (8.3)	78 (6.4)
T1	561 (11.1)	165 (10.9)	73 (9.2)	113 (9.2)
T2	1,617 (32.1)	481 (31.7)	201 (25.3)	336 (27.5)
T3	828 (16.4)	242 (15.9)	136 (17.1)	217 (17.8)
T4	1,554 (30.8)	498 (32.8)	320 (40.2)	478 (39.1)
AJCC N stage				
N0	1,454 (28.8)	383 (25.2)	165 (20.7)	311 (25.5)
N1	2,214 (43.9)	704 (46.3)	367 (46.1)	534 (43.7)
N2	633 (12.5)	198 (13.0)	111 (13.9)	125 (10.2)
N3	744 (14.7)	234 (15.4)	153 (19.2)	252 (20.6)
Treatment modality				
None	2,036 (40.4)	316 (20.8)	116 (14.6)	203 (16.6)
Surgery only	740 (14.7)	78 (5.1)	35 (4.4)	101 (8.3)
Chemo only	1,276 (25.3)	647 (42.6)	375 (47.1)	475 (38.9)
Surgery and chemo	993 (19.7)	478 (31.5)	270 (33.9)	443 (36.3)

Abbreviation: chemo, chemotherapy; HoR, hormone receptor.

eTable 8. Median Survival by M1 Subcategory, Stratified by Molecular Subtype and Histologic Grade

Molecular Subtype	Histologic Grade	M1 Subcategory	n (%)	Cancer-Specific Mortality		All-Cause Mortality	
				Median (IQR), mo	P Value	Median (IQR), mo	P Value
HoR+/HER2-	G1	M1a	405 (4.7)	NR (29.0-NR)	<.001	49.0 (26.0-NR)	<.001
		M1b	80 (0.9)	45.0 (30.0-NR)		45.0 (23.0-NR)	
		M1c	88 (1.0)	36.0 (11.0-49.0)		33.0 (8.0-49.0)	
	G2	M1a	1,638 (19.1)	54.0 (25.0-NR)	<.001	46.0 (22.0-NR)	<.001
		M1b	467 (5.4)	36.0 (15.0-NR)		31.0 (13.0-NR)	
		M1c	471 (5.5)	21.0 (5.0-39.0)		20.0 (4.0-37.0)	
	G3	M1a	1,141 (13.3)	35.0 (17.0-NR)	<.001	32.0 (16.0-NR)	<.001
		M1b	344 (4.0)	26.0 (10.0-NR)		23.0 (9.0-47.0)	
		M1c	411 (4.8)	14.0 (5.0-36.0)		14.0 (5.0-33.0)	
HoR+/HER2+	G1	M1a	17 (0.2)	56.0 (15.0-56.0)	.661	56.0 (15.0-NR)	.696
		M1b	7 (0.1)	NR (NR-NR)		NR (2.0-NR)	
		M1c	12 (0.1)	17.0 (0.0-NR)		17.0 (0.0-NR)	
	G2	M1a	304 (3.5)	NR (28.0-NR)	<.001	52.0 (25.0-NR)	<.001
		M1b	106 (1.2)	43.0 (28.0-NR)		42.0 (27.0-NR)	
		M1c	175 (2.0)	21.0 (4.0-NR)		20.0 (4.0-NR)	
	G3	M1a	423 (4.9)	NR (28.0-NR)	<.001	55.0 (26.0-NR)	<.001
		M1b	181 (2.1)	49.0 (20.0-NR)		44.0 (16.0-NR)	
		M1c	294 (3.4)	32.0 (8.0-NR)		30.0 (6.0-NR)	
HoR-/HER2+	G1	M1a	3 (0.0)	— ^a	— ^a	— ^a	— ^a
		M1b	0 (0.0)	— ^a		— ^a	
		M1c	1 (0.0)	— ^a		— ^a	
	G2	M1a	74 (0.9)	NR (24.0-NR)	<.001	NR (24.0-NR)	<.001
		M1b	62 (0.7)	47.0 (18.0-NR)		45.0 (17.0-NR)	
		M1c	72 (0.8)	18.0 (3.0-45.0)		18.0 (3.0-45.0)	
	G3	M1a	230 (2.7)	NR (18.0-NR)	<.001	NR (15.0-NR)	<.001
		M1b	145 (1.7)	33.0 (10.0-NR)		31.0 (7.0-NR)	
		M1c	209 (2.4)	19.0 (5.0-40.0)		17.0 (4.0-38.0)	
Triple-negative	G1	M1a	9 (0.1)	13.0 (13.0-25.0)	.183	13.0 (4.0-13.0)	.525
		M1b	2 (0.0)	7.0 (7.0-12.0)		7.0 (7.0-12.0)	
		M1c	4 (0.0)	4.0 (1.0-18.0)		4.0 (1.0-18.0)	
	G2	M1a	108 (1.3)	15.0 (9.0-45.0)	<.001	14.0 (6.0-32.0)	<.001
		M1b	34 (0.4)	13.0 (2.0-21.0)		13.0 (2.0-21.0)	
		M1c	63 (0.7)	5.0 (2.0-12.0)		4.0 (2.0-10.0)	
	G3	M1a	537 (6.3)	15.0 (7.0-31.0)	<.001	15.0 (7.0-29.0)	<.001
		M1b	174 (2.0)	13.0 (5.0-20.0)		12.0 (4.0-19.0)	
		M1c	291 (3.4)	8.0 (3.0-14.0)		7.0 (3.0-14.0)	

Abbreviations: HoR, hormone receptor; G, grade; IQR, interquartile range; NR, not reached.

^aNo events observed due to limited sample size.

eTable 9. Multivariate Analysis of Cancer-Specific Mortality by Treatment Modality^a

	Model 1		Model 2		Model 3	
	SHR (95% CI)	P Value	SHR (95% CI)	P Value	SHR (95% CI)	P Value
Part I: patients who did not receive RT						
M1a						
None	Ref					
Surgery only	0.65 (0.53–0.79)	<.001	Ref			
Chemo only	0.70 (0.60–0.83)	<.001	1.08 (0.88–1.33)	.462	Ref	
Surgery and chemo	0.49 (0.40–0.59)	<.001	0.75 (0.60–0.94)	.011	0.69 (0.58–0.82)	<.001
M1b						
None	Ref					
Surgery only	0.69 (0.49–0.97)	.032	Ref			
Chemo only	0.55 (0.45–0.69)	<.001	0.81 (0.57–1.13)	.207	Ref	
Surgery and chemo	0.49 (0.38–0.63)	<.001	0.71 (0.50–1.01)	.056	0.88 (0.69–1.12)	.291
M1c						
None	Ref					
Surgery only	0.65 (0.47–0.92)	.014	Ref			
Chemo only	0.45 (0.38–0.54)	<.001	0.69 (0.49–0.97)	.035	Ref	
Surgery and chemo	0.31 (0.24–0.39)	<.001	0.47 (0.32–0.68)	<.001	0.68 (0.54–0.85)	<.001
Part II: patients with TNBC who did not receive RT						
M1a						
None	Ref					
Surgery only	0.94 (0.56–1.59)	.824	Ref			
Chemo only	0.62 (0.40–0.95)	.026	0.65 (0.44–0.96)	.031	Ref	
Surgery and chemo	0.47 (0.30–0.73)	<.001	0.50 (0.34–0.73)	<.001	0.76 (0.58–0.99)	.043
M1b						
None	Ref					
Surgery only	0.78 (0.29–2.12)	.629	Ref			
Chemo only	0.27 (0.13–0.57)	<.001	0.34 (0.16–0.74)	.006	Ref	
Surgery and chemo	0.27 (0.13–0.56)	<.001	0.34 (0.16–0.73)	.006	0.99 (0.65–1.52)	.973
M1c						
None	Ref					
Surgery only	1.50 (0.75–3.02)	.251	Ref			
Chemo only	0.48 (0.31–0.73)	<.001	0.32 (0.16–0.64)	.001	Ref	
Surgery and chemo	0.21 (0.13–0.35)	<.001	0.14 (0.07–0.30)	<.001	0.44 (0.28–0.69)	<.001

Abbreviations: chemo, chemotherapy; SHR, subdistribution hazard ratio; TNBC, triple-negative breast cancer.

^aIn the multivariate analyses, a different treatment modality was selected as the reference category to perform the multiple comparisons ("no treatment" for Model 1, "surgery only" for Model 2, and "chemo only" for Model 3). Results of univariate analyses are not shown. The competing risk model was adjusted for age, sex, race/ethnicity, marital status, histologic grade, AJCC T & N category, molecular subtype, and treatment modality (data not shown).

eTable 10. Association of Primary Tumor Surgery With Mortality

Local Surgery	Patients n (%)	Univariable Analysis				Multivariable Analysis			
		Cancer-Specific Mortality		All-Cause Mortality		Cancer-Specific Mortality		All-Cause Mortality	
		SHR (95% CI)	P Value	HR (95% CI)	P Value	SHR (95% CI)	P Value	HR (95% CI)	P Value
No	5,444 (63.4)	1.86 (1.72–2.01)	<.001	1.94 (1.79–2.10)	<.001	1.59 (1.46–1.74)	<.001	1.67 (1.53–1.82)	<.001
Lumpectomy ^a	908 (10.6)	0.97 (0.85–1.10)	.594	0.96 (0.84–1.09)	.514	0.98 (0.85–1.12)	.723	0.94 (0.82–1.08)	.379
Mastectomy ^b	2,230 (26.0)	Ref		Ref		Ref		Ref	

The competing risk model was adjusted for age, race/ethnicity, marital status, histologic grade, AJCC T category, molecular subtype, use of chemotherapy, and M1 subcategory. The Cox proportional hazards model was adjusted for age, race/ethnicity, marital status, histologic grade, AJCC T & N category, molecular subtype, use of chemotherapy, and M1 subcategory.

Abbreviations: HR, hazard ratio; SHR, subdistribution hazard ratio.

^aIncludes lumpectomy, quadrantectomy, and breast-conserving surgery.

^bIncludes subcutaneous mastectomy, simple mastectomy, and modified or extended radical mastectomy.

eAppendix 1.

Validation of M1 Category Subdivision System

The association of M1 subcategories with cancer-specific or all-cause mortality was also observed in the validation and whole sets. The 3-year cumulative incidence rates of cancer-specific mortality increased across M1 subcategories: 44.1% (95% CI, 41.6%–46.7%) for M1a; 50.6% (95% CI, 46.3%–55.1%) for M1b; and 70.4% (95% CI, 66.4%–74.0%) for M1c in the validation set (Figure 1B), and 43.2% (95% CI, 41.4%–45.1%) for M1a, 52.1% (95% CI, 48.9%–55.1%) for M1b, and 71.3% (95% CI, 68.6%–73.8%) for M1c in the whole set (Figure 1C). After adjusting for clinicopathologic variables, M1 subcategories were associated with higher cancer-specific mortality both in the validation set (M1b vs M1a: SHR, 1.32; 95% CI, 1.17–1.51; $P < .001$; M1c vs M1a: SHR, 2.15; 95% CI, 1.92–2.42; $P < .001$) and the whole set (M1b vs M1a: SHR, 1.39; 95% CI, 1.27–1.53; $P < .001$; M1c vs M1a: SHR, 2.29; 95% CI, 2.11–2.48; $P < .001$) (see Table 2 and supplemental eTable 5). The 3-year all-cause mortality rates for M1 subcategories were 48.7% (95% CI, 46.1%–51.3%) for M1a, 56.8% (95% CI, 52.4%–61.0%) for M1b, and 74.7% (95% CI, 70.8%–78.2%) for M1c in the validation set and 48.3% (95% CI, 46.4%–50.1%) for M1a, 58.0% (95% CI, 54.9%–61.1%) for M1b, and 75.9% (95% CI, 73.3%–78.4%) for M1c in the whole set (Figure 1E–F). After adjusting for age at diagnosis, race/ethnicity, marital status, histologic grade, AJCC T and N stage, molecular subtype, and treatment modality, similar directions of association were observed across M1 subcategories both in the validation set (M1b vs M1a: SHR, 1.35; 95% CI, 1.20–1.53; $P < .001$; M1c vs M1a: SHR, 2.09; 95% CI, 1.88–2.33; $P < .001$) and the whole set (M1b vs M1a: SHR, 1.41; 95% CI, 1.29–1.53; $P < .001$; M1c vs M1a: SHR, 2.22; 95% CI, 2.06–2.41; $P < .001$) (see Table 2 and supplemental eTable 6).

Baseline characteristics and treatment information stratified by molecular subtypes are displayed in supplemental eTable 7. M1 subcategories were also associated with different cancer-specific mortality across the molecular subtypes in the whole set. For patients with HoR+ /HER2– breast cancer, 51% and 152% increased risk were observed for those with M1b (SHR, 1.51; 95% CI, 1.34–1.70; $P < .001$) and M1c (SHR, 2.52; 95% CI, 2.27–2.80; $P < .001$) compared with M1a disease. Similar directions of associations were observed across M1 subcategories in patients with HoR+ /HER2+ (M1b vs M1a: SHR, 1.37; 95% CI, 1.07–1.75; $P = .013$; M1c vs M1a: SHR, 2.47; 95% CI, 2.02–3.01; $P < .001$), HoR– /HER2+ (M1b vs M1a: SHR, 1.46; 95% CI, 1.07–1.98; $P = .017$; M1c vs M1a: SHR, 2.72; 95% CI, 2.09–3.52; $P < .001$), and triple-negative breast cancer (M1b vs M1a: SHR, 1.39; 95% CI, 1.15–1.68; $P = .006$; M1c vs M1a: SHR, 2.23; 95% CI, 1.92–2.60; $P < .001$) (see supplemental eFigure 2). Similarly, significantly different median survival was observed across M1 subcategories when stratified by molecular subtypes and histologic grades (see supplemental eTable 8).