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Treatment Patterns and Mortality Risk among Elderly Patients with Metastatic Triple Negative Breast Cancer in the United States: An Observational Cohort Study Using SEER-Medicare Data

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Abstract

Purpose: Triple negative breast cancer is more aggressive than other breast cancer subtypes and accounts for up to 20% of all breast cancers. Despite the poorer prognosis, there are no approved targeted treatments available and chemotherapy remains the only choice. We examined treatment patterns and outcomes among elderly metastatic triple-negative breast cancer (mTNBC) patients in routine clinical practice. *Methods*: Patients were identified from the linked SEER-Medicare database between 1/1/2001 and 12/31/2013 and included *de novo* Stage IV (n = 776) and patients with distant metastasis followed an initial diagnosis of Stage I - III disease (n = 1851). Kaplan-Meier analyses and time-varying Cox proportional hazards regression were used to assess overall survival (OS). *Results*: The mean age at metastatic diagnosis was 77.6 years and 1259 (48%) patients received chemotherapy. Compared to <70 year olds, ≥70 year olds had worse performance status, higher comorbidity burden, and were less likely to receive chemotherapy (45% vs. 66%). Patients treated with chemotherapy had increased OS compared to untreated patients, and the survival advantage was more pronounced in the <70 year olds with a 6-month longer unadjusted OS compared to the ≥70 cohort (log rank p < 0.0001). This finding was supported in the adjusted multivariate model which showed a 46% increased risk of death for untreated patients in the <70 year olds and a 17% increased risk of death for untreated patients in the ≥70 year olds (vs. treated). *Conclusions*: In this real-world analysis, 48% of elderly mTNBC patients did not receive chemotherapy and a greater proportion were

untreated in the ≥70 year old cohort (55%). Although the survival benefits of chemotherapy were greater in the younger cohort, the benefits of treatment persisted in ≥70 year olds. These findings suggest opportunities exist to improve the clinical treatment of elderly mTNBC patients.

Keywords

Triple Negative Breast Cancer, Elderly Patients, Chemotherapy, Survival

1. Introduction

Breast cancer is the most common type of cancers affecting women in the United States, accounting for approximately 252,710 new cases in 2017 [1]. The risk increases with age, and about one-third of female breast cancers are diagnosed in patients older than 70 years of age [2]. Approximately 6% of women will present with metastatic disease at diagnosis (*de novo* Stage IV disease) and roughly 30% of women diagnosed with early stage disease will experience a distant recurrence [3]. The majority of deaths from breast cancer result from recurrent or metastatic disease. In 2017, there will be an estimated 40,610 deaths, making breast cancer the second leading cause of deaths from cancers among women [1].

The triple-negative breast cancer (TNBC) subtype accounts for 12% - 17% of all breast cancers and is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) [4]. Although less than 6% of breast cancers are associated with breast cancer gene (BRCA) mutations, around 20% of TNBC patients have a BRCA mutation [5]. TNBC is typically diagnosed at an earlier age, is more prevalent among Hispanic and African women, and is more aggressive with a high risk of metastasis and deaths within 5 years after diagnosis [4] [6] [7]. The triple-negative phenotype is unresponsive to endocrine therapy, and until recently, there have been no targeted therapies approved by the FDA, making chemotherapy the only treatment option.

The therapeutic goal at this advanced stage of disease is palliative: to prolong survival and improve quality of life. The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer have no age limit recommendation for chemotherapy but state that there are limited data to make chemotherapy recommendations for patients older than 70 years and that treatment should be individualized with consideration of comorbid conditions [8]. There are limited data among patients older than 70 years as chemotherapy clinical trials usually include younger and healthier cancer patients, and fewer than 4% of clinical trial participants are older than 70 [9] [10]. Age has been shown to be a barrier to receiving chemotherapy due to physician and patient concerns about treatment toxicity [11] [12] [13]. Elderly patients have poorer outcomes compared to younger patients, and this may be related to "under-treatment" in the elderly population [2] [14].

Few population-based studies of treatment patterns and survival outcomes among metastatic TNBC patients exist. It is important to understand whether the benefits of chemotherapy are maintained in elderly mTNBC patients in the real-world setting. The objective of this study was to assess chemotherapy treatment patterns and outcomes to better understand the age-related differences among TNBC patients and the unmet need in a real-world setting.

2. Materials and Methods

2.1. Data Source

The linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database combines cancer registry data with administrative Medicare files from the Centers for Medicare and Medicaid Services. It contains more than 3.3 million persons with cancer. SEER is a nationally representative collection of population-based cancer registries from diverse geographic areas covering approximately 26% of the United States population. The majority of persons aged 65 years and older in SEER are successfully matched to their Medicare enrollment files [15]. Details of the SEER-Medicare database have been published previously [15]. Briefly, the database combines clinical, demographic, cancer diagnosis, survival, and cause of death information with medical claims (hospital, physician, outpatient, home health, and hospice bills) for adults 65 years and older with cancer. All Medicare beneficiaries receive Part A coverage (inpatient care, skilled nursing, home healthcare and hospice care) and approximately 95% of beneficiaries subscribe to Part B (outpatient and physician services). The database linkage used in this study included cancer cases diagnosed until 2011 with Medicare claims through 2013. Institutional review board (IRB) approval was waived because the National Institutes of Health's Office of Human Subjects Research has determined that analyses using SEER-Medicare data are exempt from requiring further IRB review and approval.

2.2. Study Population

Patients with a first primary breast cancer were identified using the SEER variables indicating the cancer site and order of incident cancer diagnoses. Data on ER and PR status have been collected since 1990 and HER2 since 2010 in SEER. HER2 status was not available before the year 2010, so the presence of Medicare claims for HER2 targeted therapies, *i.e.*, trastuzumab (Herceptin®, Roche) and lapatinib (Tykerb®, Glaxo Smith Kline) were used as a proxy for HER2 positive status, and absence of these claims was assumed to indicate HER2 negative status. A case was defined as triple-negative if ER, PR, and HER2 were negative. Staging of primary breast cancer was based on the American Joint Committee on Cancer Criteria (AJCC), 6th edition in SEER. Since SEER does not include information on disease progression, Medicare claims data were used to identify patients with distant metastasis following an initial diagnosis of Stage I - III breast cancer. The first-listed International Classification of Disease, 9th Revi-

sion, Clinical Modification (ICD-9-CM) code indicating a secondary cancer (197.XX–198.XX), excluding breast (198.81, 198.82) and lymph node (196.XX) [16] [17], were used to classify patients in the non-*de novo* metastatic group.

See **Figure 1** for the schematic of the inclusion/exclusion process. Patients were diagnosed with a first primary metastatic triple-negative breast cancer between January 1, 2001 and December 31, 2011, ≥66 years at the time of diagnosis, and enrolled in Medicare Parts A and B for a full 12 months prior to diagnosis date. Patients were excluded if breast cancer was diagnosed at the time of death or autopsy, and if enrolled in a health maintenance organization (HMO) any time within the 12 months prior to diagnosis as HMO claims are unavailable in the dataset. There were 776 *de novo* Stage IV patients and 1851 patients with non-*de novo* metastatic disease identified using the algorithm described above.

2.3. Study Variables

Key study measures include patient demographics (age, race/ethnicity, marital status, income, education level and geographic region), clinical characteristics (tumor characteristics, comorbidity burden, poor performance indicators), and treatment information. Performance status measures, such as Eastern Cooperative Oncology Group (ECOG) are not available in the dataset so Medicare claims were used to identify poor performance indicators (PPI) which include oxygen and related respiratory supplies, wheelchair and supplies, home health agency services, and skilled nursing facility services occurring in the 12 months prior to metastatic diagnosis date [18]. The National Cancer Institute (NCI) comorbidity index [19], the gold-standard in SEER-Medicare, was used to assess comorbidity burden using diagnosis and procedure codes in the Medicare claims files to identify the 15 non-cancer comorbidities from the Charlson Comorbidity Index [20] that occurred in the 12 months prior to metastatic diagnosis date.

In the Medicare claims files, ICD-9-CM procedure codes were used to identify chemotherapy administration while the Healthcare Common Procedural Coding System (HCPCS) "J" codes were used to identify the specific intravenous chemotherapy administered [21]. The first claim for chemotherapy was required to appear within six months of metastatic diagnosis date for a patient to be considered in the "treated" cohort. Patients with a history of breast cancer surgery (lumpectomy and mastectomy) and radiation therapy, were identified by searching Medicare claims for ICD-9 procedure codes and Current Procedural Terminology (CPT) procedure codes from initial diagnosis date of first primary breast cancer through the end of follow-up.

2.4. Statistical Analysis

Patient characteristics were compared by age and treatment status using the Chi-square test for categorical variables and ANOVA or t-test for continuous variables, with tests of significance measured at a p-value < 0.05. The primary endpoint, overall survival (OS) was measured from date of metastatic diagnosis

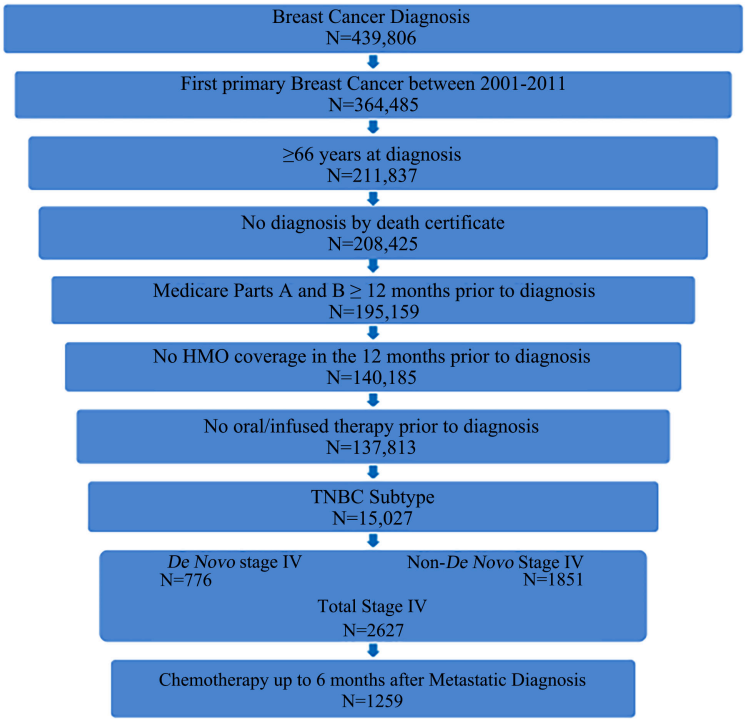


Figure 1. Cohort inclusion/exclusion criteria.

to date of death; if still alive, patients were censored at the end of the follow-up period (December 31, 2013) or until Medicare claims were no longer available. Unadjusted overall survival was assessed using Kaplan-Meier survival analysis. A time-varying Cox proportional hazards regression model with chemotherapy treatment as a time-dependent factor was used to account for variation in treatment initiation between patients and to minimize the introduction of immortal time bias into the analysis (period of follow-up time during which death cannot occur) [22]. In the time-varying Cox model, all patients belong to the "not treated" group and only switched to the "treated" group at the time of treatment receipt. This Cox model is used to explore predictors of overall risk of death adjusting for potential confounding variables which were selected based on *a priori* beliefs that these factors are associated with receipt of treatment. The fully adjusted model included age, race, marital status, education, income, geographic region, initial stage at diagnosis, year of diagnosis, poor performance, comorbidity score, radiotherapy, surgery, and chemotherapy. In these survival analyses, comparisons were made between the chemotherapy treated versus not treated patients, stratified by age < 70 years and ≥70 years. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc., Cary, North Carolina).

3. Results

3.1. Patient Characteristics

The demographic and clinical characteristics of the cohort are presented in Ta-

ble 1. The mean age at metastatic diagnosis was 77.6 years. The majority of metastatic patients were in the older cohort of ≥70 year olds (86%) compared to the younger cohort of <70 year olds (14%). Patients in the older cohort were more likely to be white (78% vs. 71%) while the younger cohort had a higher proportion of patients of African ancestry (25% vs. 16%). Patients in the older cohort were also more likely to be widowed (46% vs. 25%), have a higher education level, and higher income level compared to their younger counterparts. In regards to clinical characteristics, patients in the younger cohort were more likely to be diagnosed with *de novo* Stage IV disease (42% vs. 28%) while the older cohort contained more patients who experienced distant metastasis following an initial diagnosis of Stage I - III breast cancer (72% vs. 58%). Compared to the younger cohort, the patients in the older cohort had poorer performance and a higher comorbidity burden.

3.2. Treatment Patterns

There was no difference in radiotherapy treatment rates between age cohorts, however patients in the older cohort were more likely to have a history of breast cancer surgery compared to the younger cohort. Overall, about 48% of TNBC patients received treatment with chemotherapy within 6 months after metastatic diagnosis, and the proportion treated was higher in the younger cohort compared to the older cohort (66% vs. 45%). Cyclophosphamide (29%), paclitaxel (23%), docetaxel (23%), doxorubicin (20%) carboplatin (11%) and capecitabine (10%) -based regimens were the most common first-line chemotherapies administered in the metastatic setting (Table 2). Patients in the older cohort were more likely to receive capecitabine-based therapy; all other treatment regimens were more common in the younger cohort of patients.

3.3. Survival

The median unadjusted OS was 8.8 months (95% CI: 8.0 - 9.8) for all metastatic TNBC patients (Figure 2). Patients who received treatment with chemotherapy had a higher unadjusted median OS (12.8 months, 95% CI: 11.5 - 13.9) compared to untreated patients (4.9 months, 95% CI: 4.2 - 5.8). When stratifying by age, the survival advantage was more pronounced among treated patients in the younger cohort (17.7 months, 95% CI: 13.4 - 24.8 vs.) compared to treated patients within the older cohort (11.7 months, 95% CI: 10.5 - 13.4 vs. 5.0 months, 95% CI: 4.2 - 5.9).

The time-varying Cox model (Table 3) showed no statistically significant mortality risk difference for untreated vs. treated patients in the overall cohort of metastatic patients (HR = 1.095; 95% CI = 1.00 - 1.20). However, when stratifying by age group, a 46% increased risk of death for untreated patients in the <70 year old cohort and a 17% increased risk of death for untreated patients in the ≥70 year olds (vs. chemotherapy treated patients) were observed. Other factors in the model found to be predictive of increased mortality risk included: increasing initial stage at diagnosis, increasing comorbidity score, and presence of

PPI. Prior radiotherapy and breast cancer surgery were associated with lower mortality risks.

Table 1. Demographic and clinical characteristics by age.

	Total metastatic N = 2627		<70 years N = 359		≥70 years N = 2268		p value
	n	%	n	%	n	%	
Mean age (95% CI)	77.57	77.3 - 77.8	67.67	67.6 - 67.8	79.14	78.9 - 79.4	<0.0001
Race/ethnicity							
White	2032	77.4	255	71.0	1777	78.4	0.0002
Black	460	17.5	90	25.1	370	16.3	
Other/unknown	135	5.1	14	3.9	121	5.3	
Marital status							
Single	219	8.3	48	13.4	171	7.5	<0.0001
Married	946	36.0	162	45.1	784	34.6	
Separated/divorced	250	9.5	44	12.3	206	9.1	
Widowed	1134	43.2	90	25.1	1044	46.0	
Unknown	78	3.0	15	4.2	63	2.8	
% of adults with some education							
0 - 50	906	34.5	144	40.1	762	33.6	0.0077
51 - 100	1665	63.4	203	56.5	1462	64.5	
Unknown	56	2.1	12	3.3	44	1.9	
Median income quartiles							
1-Low	643	24.5	118	32.9	525	23.1	0.0002
2	644	24.5	85	23.7	559	24.6	
3	643	24.5	77	21.4	566	25.0	
4-High	641	24.4	67	18.7	574	25.3	
Unknown	56	2.1	12	3.3	44	1.9	
Geographic region							
Midwest	347	13.2	54	15.0	293	12.9	0.0123
Northeast	187	7.1	28	7.8	159	7.0	
South	958	36.5	103	28.7	855	37.7	
West	1135	43.2	174	48.5	961	42.4	
Stage at initial diagnosis							
Stage I	678	25.8	68	18.9	610	26.9	<0.0001
Stage II	785	29.9	91	25.3	694	30.6	
Stage III	388	14.8	50	13.9	338	14.9	
Stage IV	776	29.5	150	41.8	626	27.6	
PPI							
No	2288	87.1	324	90.3	1964	86.6	0.0550

Continued

Yes	339	12.9	35	9.7	304	13.4	
NCI comorbidity score							
0	1483	56.5	227	63.2	1256	55.4	0.0116
1	643	24.5	72	20.1	571	25.2	
2	257	9.8	24	6.7	233	10.3	
≥3	244	9.3	36	10.0	208	9.2	
Radiation therapy							
No	1082	41.2	136	37.9	946	41.7	0.1709
Yes	1545	58.8	223	62.1	1322	58.3	
Breast cancer surgery							
No	544	20.7	108	30.1	436	19.2	<0.0001
Yes	2083	79.3	251	69.9	1832	80.8	
Chemotherapy							
No	1368	52.1	123	34.3	1245	54.9	<0.0001
Yes	1259	47.9	236	65.7	1023	45.1	

Abbreviations: NCI: National Cancer Institute; PPI: poor performance indicators.

Table 2. First-line chemotherapy in metastatic setting.

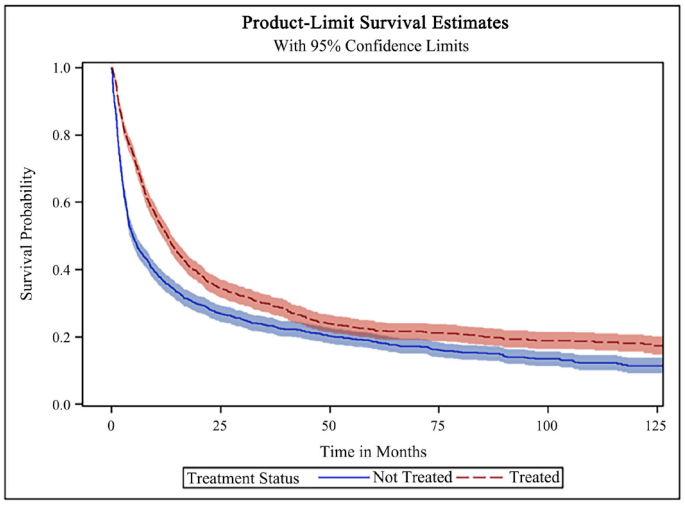
Chemotherapy	Total treated N = 1259		<70 years N = 236		≥70 years N = 1023	
	n	(%)	n	(%)	n	(%)
Capecitabine (xeloda)	130	10.3	14	5.9	116	11.3
Carboplatin (paraplatin)	143	11.4	30	12.7	113	11.0
Cyclophosphamide (cytoxan)	360	28.6	97	41.1	263	25.7
Docetaxel (taxotere)	290	23.0	73	30.9	217	21.2
Doxorubicin (adriamycin)	256	20.3	79	33.5	177	17.3
Fluorouracil (adrucil)	112	8.9	15	6.4	97	9.5
Gemcitabine (gemzar)	87	6.9	18	7.6	69	6.7
Nab-paclitaxel (abraxane)	68	5.4	**	**	**	**
Paclitaxel (taxol)	295	23.4	60	25.4	235	23.0
Paclitaxel (taxol) + other	204	16.2	45	19.1	159	15.5
AC-T: [AC + paclitaxel (taxol) or docetaxel (taxotere)]	109	8.7	39	16.5	70	6.8
AC: [doxorubicin (adriamycin) + cyclophosphamide (cytoxan)]	213	16.9	71	30.1	142	13.9
TC: [docetaxel (taxotere) + cyclophosphamide (cytoxan) or carboplatin	143	11.4	38	16.1	105	10.3
Unknown chemotherapy	73	5.8	12	5.1	61	6.0

Note: Patients may receive more than one metastatic 1L chemotherapy so percentages will add to more than 100%; **Cells with counts of less than 11 are suppressed in compliance with the National Cancer Institute data use agreement for small cell sizes.

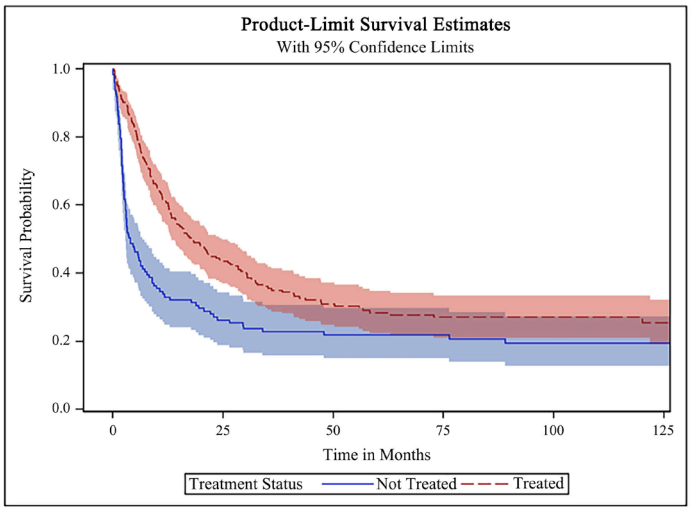
Table 3. Time-varying Cox Model.

	Total metastatic[a] N = 2627		<70 years[a] N = 359		≥70 years[a] N = 2268	
Chemotherapy	HR	95% CI	HR	95% CI	HR	95% CI
Treated	ref		ref		ref	
Not treated	1.095	1.00 - 1.20	1.455	1.08 - 1.96	1.166	1.06 - 1.29
Age at diagnosis						
66 - 70	ref	ref				
71 - 75	1.095	0.95 - 1.26				
76 - 80	1.333	1.16 - 1.54				
>80	1.707	1.48 - 1.96				
Race/ethnicity						
White	ref		ref		ref	
Black	0.863	0.76 - 0.98	0.731	0.52 - 1.02	0.851	0.74 - 0.98
Others	0.795	0.64 - 0.99	0.760	0.36 - 1.60	0.781	0.62 - 0.98
Stage at initial diagnosis						
Stage I	ref		ref		ref	
Stage II	1.196	1.05 - 1.36	1.193	0.76 - 1.87	1.208	1.06 - 1.38
Stage III	1.424	1.22 - 1.66	1.825	1.10 - 3.02	1.455	1.24 - 1.71
Stage IV	1.609	1.40 - 1.85	2.170	1.38 - 3.42	1.564	1.35 - 1.82
PPI						
No	ref		ref		ref	
Yes	1.180	1.03 - 1.35	1.122	0.71 - 1.79	1.215	1.05 - 1.41
NCI comorbidity score						
0	ref		ref		ref	
1	1.236	1.11 - 1.38	0.773	0.55 - 1.09	1.304	1.16 - 1.46
2	1.046	0.90 - 1.22	1.268	0.74 - 2.17	1.055	0.90 - 1.24
≥3	1.424	1.21 - 1.67	1.907	1.24 - 2.94	1.339	1.12 - 1.60
Radiotherapy						
No	ref		ref		ref	
Yes	0.809	0.74 - 0.89	0.972	0.73 - 1.29	0.763	0.69 - 0.84
Breast cancer surgery						
No	ref		ref		ref	
Yes	0.618	0.55 - 0.70	0.438	0.32 - 0.61	0.663	0.58 - 0.76

Abbreviations: HR: Hazard Ratio; CI: confidence interval; NCI: National Cancer Institute; PPI: poor performance indicators. [a]Model also includes marital status, education, income, geographic region, and year of diagnosis.



(a)



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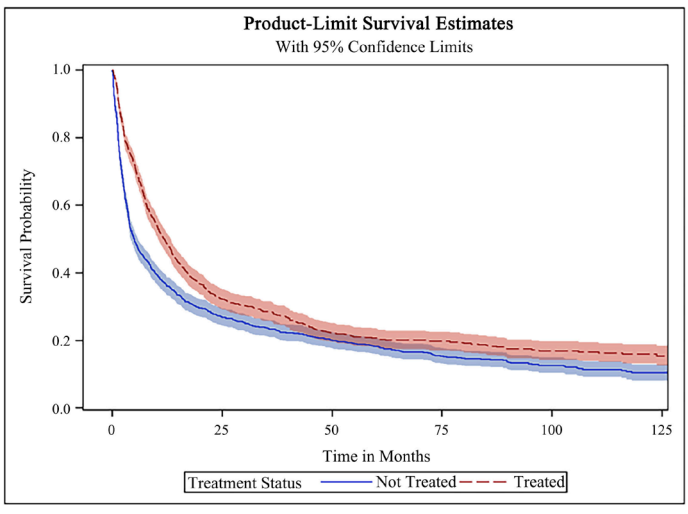

(c)

Figure 2. Unadjusted overall survival by treatment status. (a) All metastatic patients; (b) <70 year olds; (c) ≥70 year olds.

3.4. *De Novo* vs. Non-*De Novo* Metastatic Treated Subgroup Analysis

A subgroup analysis of the chemotherapy-treated cohort was performed to compare treatment patterns and outcomes between *de novo* patients (N = 415) and non-*de novo* patients (N = 844) who experienced distant metastasis or relapsed disease following an initial diagnosis with Stage I - III disease. Treatment for early breast cancer was defined as having received chemotherapy within 6 months after initial Stage I - III diagnosis. Patients with non-*de novo* metastatic disease were stratified into two groups: those who relapsed or progressed ≤ 12 months after completing treatment for early breast cancer (fast relapse; N = 250) and those who relapsed or progressed > 12 months after completing treatment for early breast cancer (slow relapse; N = 594). We found that patients who relapse slow were older and more likely to be initially diagnosed with Stage I disease compared to patients who relapse fast (Table 4). Overall, non *de-novo* metastatic patients were more likely to have prior radiotherapy and breast cancer

Table 4. Demographic and clinical characteristics by metastatic group.

	Non-*de novo* metastatic		*De Novo* metastatic N = 415	p value
	Fast relapse[a] N = 250	Slow relapse[b] N = 594		
Mean age (95% CI)	74.5 (73.8 - 75.3)	76.1 (75.6 - 76.6)	74.7 (74.1 - 75.3)	<0.0001
Initial stage at diagnosis, %				
Stage I	27	35	-	<0.0001
Stage II	42	43	-	
Stage III	32	22	-	
Stage IV	-	-	100	
Radiotherapy, %				
No	28	25	50	<0.0001
Yes	72	75	50	
Surgery, %				
No	8	6	51	<0.0001
Yes	92	94	49	
Chemotherapy, %				
Capecitabine	5	11	13	0.0086
Carboplatin	10	13	11	0.4948
Cyclophosphamide	25	32	26	0.0397
Docetaxel	23	21	26	0.2359
Doxorubicin	16	23	19	0.0611
Paclitaxel	18	24	27	0.0217
Median (IQR) duration of chemo, days	58 (30 - 128)	116 (72 - 164)	102 (50 - 149)	<0.0001
Median (95% CI) OS, months	12.1 (9.4 - 16.0)	19.9 (16.4 - 24.6)	7.8 (6.7 - 8.9)	<0.0001

[a]Patients who relapsed or progressed ≤ 12 months after completing treatment for early breast cancer; [b]Patients who relapsed or progressed > 12 months after completing treatment for early breast cancer.

surgery compared to patients with *de novo* Stage IV disease. Patients who relapse slow were more likely to receive cyclophosphamide and doxorubicin while docetaxel and paclitaxel were more commonly given to patients with *de novo* Stage IV disease. Median duration of chemotherapy was shortest for patients who relapse fast (58 days, IQR: 30 - 128), followed by patients with *de novo* Stage IV disease (102 days, IQR: 50 - 149), and longest for patients who relapse slow (116 days, IQR: 72 - 164; $p < 0.0001$). The median unadjusted OS was shortest for patients with *de novo* Stage IV disease (7.8 months, 95% CI: 6.7 - 8.9), followed by patients who relapse fast (12.1 months, 95% CI: 9.4 - 16.0), and longest for patients who relapse slow (19.9 months, 95% CI: 16.4 - 24.6).

4. Discussion

This large population-based study showed that elderly patients with metastatic TNBC were frequently untreated with over half not receiving chemotherapy. The study also demonstrated that patients who were 70 years and older were more likely to suffer from pre-existing comorbidities and had poorer performance compared to patients younger than 70 years old. These findings are consistent with other studies that have shown older age and co-morbidities are associated with less aggressive treatment [23] [24]. After adjusting for comorbidity burden, poor performance and other patient characteristics in the multivariate survival models, a 46% increased mortality risk for untreated patients compared to chemotherapy treated patients in the younger cohort of less than 70 year olds was seen. The benefit of chemotherapy persisted in the older cohort but was not as prominent as that seen in the younger cohort. Data from clinical trials suggest that older and younger women may experience similar survival benefits from chemotherapy, and age alone should not contraindicate the use of chemotherapy in older women who are in good health [25].

Chemotherapy has been the mainstay of systemic treatment for TNBC but there is no gold-standard regimen. Studies suggest that taxanes in particular have significant activity in the treatment of TNBC [26] [27] [28]. This study showed that taxane-based chemotherapy regimens, as well as cyclophosphamide- and anthracycline-based regimens were most commonly used in this time period. Further, patients in the younger cohort were more likely to receive chemotherapy across most regimen types with the exception of capecitabine, the use of which was more prevalent in the older cohort. One prior study showed that 35% of patients older than 65 years were offered chemotherapy and they were twice as likely as younger patients to reject chemotherapy out of fear for side effects [29]. Moving forward, it will be important to design clinical trials to address the therapeutic challenges that exist in this cohort of patients. While endocrine and HER2-targeted therapy are ineffective in this patient population, the use of immunotherapy has been gaining traction in TNBC, which has been shown to be more immunogenic compared to other breast cancer subtypes [30]. Early clinical experience with programmed cell death (PD-1) antibody pembrolizumab as well as the programmed cell death ligand (PD-L1) antibody atezoli-

zumab show promising results in clinical trials [31] [32] [33].

This study also found that a history of radiotherapy and breast cancer surgery were associated with lower mortality risks. Age-related declines in major physiologic functions may impact a patient's ability to tolerate surgery, radiation, and cytotoxic chemotherapy [2]. However, studies that examined the predictors of receiving surgery and radiation found that increasing age was associated with substandard therapy independent of performance status or comorbidities, suggesting that physicians may be under-treating otherwise "healthy" elderly women [2].

In the subset analysis of treated patients, women with relapsed disease had higher unadjusted OS compared to women with *de novo* Stage IV disease. One prior study comprised of younger patients (median age 50 - 52 years) of all breast cancer subtypes found the opposite effect [34]. However, after restricting their analysis to women with at least a 5-year disease free interval (time from primary non-metastatic diagnosis to first distant metastasis), relapsed patients exhibited a statistically significant longer OS compared to *de novo* Stage IV patients [34]. In the current study it was found that patients who relapse slow (disease-free interval of >12 months) had superior prognostic outcomes compared to patients who relapse fast (disease-free interval of <12 months). Disease-free interval or time to disease progression appears to be an important prognostic variable among women with relapsed disease [34].

Strengths & Limitations

Clinical trial participants are often not representative of individuals in the real-world, and the SEER-Medicare database is therefore an invaluable tool for studying treatment patterns and long-term outcomes among elderly patients who have been historically underrepresented in clinical trials. The dataset includes a large sample size with diverse geographic representation of metastatic TNBC patients, and contains longitudinal claims data regardless of residence or service area from the time a person is eligible for Medicare until death. However, there are a few data limitations that should be addressed. The SEER registries do not collect follow-up information on disease progression after diagnosis, therefore metastasis or relapse could not be directly identified in the dataset. We used ICD-9 diagnosis codes indicative of secondary cancer in the Medicare claims to identify relapsed/progressed patients. However, using this method may result in incomplete or inaccurately coded information since these secondary cancer codes do not impact the amount of reimbursement to the provider. Several population-based studies have examined the completeness and accuracy of using ICD-9 diagnosis codes for secondary neoplasm and have reported considerable variability in the sensitivity, specificity and positive predictive value [35] [36]. Since the SEER registry did not have information on HER2 status prior to the year 2010, there was a large amount of missing data on HER2 status. Claims for HER2 targeted therapies were utilized as a proxy for HER2 status given that

Medicare does not pay for targeted therapy without a positive HER2 test result. However, it's possible that patients who tested HER2 positive did not receive targeted therapy and could have been misclassified into the HER2 negative group. The SEER-Medicare database also does not include measures of performance status. Claims for oxygen and related respiratory supplies, wheelchair and supplies, home health agency services, and skilled nursing facility services were included as a surrogate for poor performance; however this may not adequately assess performance status for all patients in the study. Finally, information regarding treatment patterns and characteristics of patients enrolled in HMO or fee-for-service plans were not available since Medicare does not collect these data. Treatment patterns and survival outcomes may differ between these alternative health care plans and Medicare enrollees.

5. Conclusion

In this real-world analysis, roughly half of elderly TNBC patients did not receive chemotherapy following their metastatic diagnosis. Although the survival benefits of chemotherapy were stronger in the younger cohort, the benefits of treatment were maintained among ≥70 year olds who were also less likely to receive chemotherapy. This may reflect under-treatment among elderly women with TNBC, potentially adversely affecting their prognosis. Elderly patients should be given guideline-based treatment in the absence of other reasons for withholding treatments. These results extend the findings from clinical trials conducted among younger women to an elderly breast cancer population, provide further insights into the natural history of the disease and remain unmet need in a real-world setting.

Authors' Contributions

Study Concepts: SS-H, CR.
Study Design: SS-H, PB, AS, PC, FM, CR.
Data Acquisition: SS-H, CR.
Quality Control of Data and Algorithms: SS-H, FM.
Data Analysis and Interpretation: SS-H, PB, AS, PC, FM, CR.
Statistical Analysis: SS-H, FM.
Manuscript Preparation: SS-H.
Manuscript Editing: SS-H, PB, AS, PC, FM, CR.
Manuscript Review: SS-H, PB, AS, PC, FM, CR.

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agement Services, Inc. (Silver Spring, MD), and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

Conflicts of Interest

PB, AS, PC and CR are employees of Genentech and shareholders of Roche. SS-H and FM work for Q.D. Research in a research and consulting capacity.

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