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Association of Guideline-Concordant Initial Systemic Treatment with Clinical and Economic Outcomes Among Older Women with Metastatic Breast Cancer in the United States

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Abstract

Purpose: We examined guideline-concordant initial systemic treatment among women with metastatic breast cancer, its predictors, and if guideline-concordant treatment was associated with mortality, healthcare utilization and Medicare expenditures.

Methods: This retrospective observational cohort study was conducted using the Surveillance, Epidemiology, End Results-Medicare linked database. Women aged 66–90 years diagnosed with metastatic breast cancer during 2010–2013 (N=1,282) were included. The National Comprehensive Cancer Network treatment guidelines were used to determine the guideline-concordant initial systemic treatment following cancer diagnosis. A logistic regression analysis was conducted to examine significant predictors of guideline-concordant treatment. Generalized linear regressions were used to examine the association between guideline-concordant treatment and healthcare utilization and average monthly Medicare expenditures.

Results: About 74% of the study cohort received guideline-concordant initial systemic treatment. Women who received guideline-concordant treatment were significantly more likely to be comparatively younger ($p<0.05$), were married/partnered ($p=0.0038$), had HER2 positive tumors,

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and had good performance status. Adjusted hazards ratios for all-cause (2.364, p<0.0001) and breast-cancer specific mortality (2.179, p<0.0001) were higher for women who did not receive guideline-concordant treatment. Rates of healthcare utilization were also higher for women not receiving guideline-concordant treatment. Average monthly Medicare expenditures were 100.4% higher (95% confidence interval: $77.3%−126.5%) for women who did not receive guideline-concordant treatment compared to those who received guideline-concordant treatment (p<0.0001).

Conclusion: One fourth of the study cohort did not receive guideline-concordant initial systemic treatment. Guideline-concordant initial treatment was associated with reduced mortality, and lower healthcare utilization and Medicare expenditures in women with metastatic breast cancer.

Keywords

Guideline-Concordant Initial Treatment; Metastatic Breast Cancer; Survival; Medicare expenditures; Predictors

INTRODUCTION

Development of evidence-based National Comprehensive Cancer Network (NCCN) guidelines has optimized cancer care and is being used as a marker for high quality care.[1] Despite the establishment of treatment guidelines, not all patients receive guideline-concordant cancer care. Vulnerable patient subgroups such as racial/ethnic minorities, socioeconomically disadvantaged individuals, and older adults are less likely to receive guideline-concordant cancer care.[2–5] Identifying disparities in adherence to treatment guidelines and its effect on cancer outcomes is essential in understanding why certain patient subgroups do not receive recommended care and may die prematurely. In addition to poorer clinical outcomes, receipt of non-guideline concordant cancer care can also contribute to higher cancer care expenditures.[6,7] Several payers are implementing programs that limit the reimbursement for non-guideline-based care in order to control expenditures and minimize treatment variability.[8]

In the United States, survival rates of breast cancer (BC) have improved significantly over the past few years,[9] however the risk of mortality is 46% higher in untreated patients compared to those treated with chemotherapy.[10] Data about guideline-concordant care and its impacts on outcomes among patients with metastatic BC (MBC) are limited. The treatment of patients with MBC is complex due to multiple guideline-concordant regimens recommended per the NCCN guidelines per tumor status. One study found that 19% of older women diagnosed with *de novo* MBC during 2007–2013 did not receive guideline-concordant treatment. In addition, non-guideline-concordant treatment was significantly associated with higher Medicare expenditures, and also higher healthcare utilization and a slightly improved survival but the associations were not significant.[7] However, data about human epidermal growth factor receptor 2 (HER2) status was not available in the SEER prior to 2010, and women in the study with unknown HER2 status who received specific treatments for HER2+ or HER2- disease were assumed to be guideline-concordant. Another study that used SEER data for cases diagnosed during 2007–2013 found that 18% of women with MBC did not receive guideline-concordant treatment and also found that non-concordance to cancer treatment was associated with increased costs to Medicare and

increased healthcare utilization.[11] However, this study included older women with secondary metastases only. Additionally, the association between non-guideline-concordant treatment and hospice use was not evaluated in either of these studies. Yet another study that used SEER data from 2010–2011 found that 23% of older women with de novo MBC did not receive initial systemic treatment, half of the cases with triple-negative MBC did not receive initial systemic therapy, while 18% with hormone receptor (HR) positive disease did not receive an initial endocrine therapy.[12] Additionally, a higher proportion of the patient population who did not receive systemic cancer treatment utilized more healthcare services including hospitalizations and hospice use, and died earlier than those who received systemic therapy. Furthermore, in one of prior studies using the SEER-Medicare data, we examined disparities and magnitude of disparities in guideline-concordant treatment specifically among women with HER2-positive MBC and found that about 23% did not receive guideline-concordant initial systemic treatment and disparities existed by HR status of the tumor.[13] The former three studies accounted for age and comorbidities, which are strong confounders to address when assessing the impact of guideline-concordant treatment on outcomes. However, performance status was not captured, which is an important factor associated with both guideline-concordant cancer treatment, especially for advanced cancer,[14] and health outcomes. Additionally, aspects of healthcare access such as availability of oncology hospitals in the area of patient's residence, were not accounted for in the previously published studies. The literature suggests that area-level availability of healthcare resources can play a significant role in improving breast cancer outcomes by increasing the likelihood of women's receipt of cancer treatment.[15,16] It is likely that lower availability of healthcare access in terms of oncology hospitals may adversely affect outcomes especially for the patients with metastatic disease.

Women age 65 and older experience substantial BC burden and are also undertreated frequently.[7,17] Hence, it is critical to examine how guideline-concordant treatment in older women with MBC impacts their outcomes. Considering all these factors, the objective of this study was to evaluate the impact of guideline-concordant treatment in older patients with *de novo* MBC on survival, Medicare expenditures, and healthcare utilization, within a multivariable framework.

METHODS

Study Design and Data Source

We conducted a longitudinal retrospective cohort study using the SEER-Medicare linked dataset.[18] Using the state and county level information, we linked the Area Resource File to the SEER-Medicare dataset to obtain census track data on income, education, and hospitals offering oncology services.[19]

Study Cohort

We included women aged 66–90 years at the diagnosis of the first pathologically confirmed *de novo* MBC (SEER site recode 46, AJCC stages IV, IVNOS, IVA, IVB, IVC)[20] during 2010–2013 and who were enrolled in the Medicare fee-for-service program. We excluded women who were not continuously enrolled in Medicare parts A and B during the 12 months

prior to the date of cancer diagnosis through at least six months following the date of cancer diagnosis, end of enrollment, or death, or were diagnosed with a death certificate or autopsy.

Measures

Key Independent Variable: Guideline-Concordant Treatment—We used the National Comprehensive Cancer Network (NCCN) guidelines to determine concordance with initial treatment according to HER2 and HR status, received within six months of cancer diagnosis. As data from women diagnosed during 2010–2013 were included, we used all the versions of the NCCN guidelines published during this period to determine recommended treatment strategies for each particular year.[21–24] If a woman received the initial treatment listed on the NCCN guidelines (Supplemental Table 1), then she was considered to have received guideline-concordant treatment. We identified endocrine therapies, infused or oral chemotherapies, and the HER2-targeted therapies using the J-codes and the National Drug Codes (NDC) from the Medicare claims files. We categorized the key independent variable as guideline-concordant treatment and non-guideline-concordant treatment.

Survival—We assessed survival time in days from the date of cancer diagnosis until death, end of Medicare enrollment, or end of study period (i.e. December 31, 2014), whichever occurred first. To assess breast-cancer specific survival, women with MBC who were alive until the end of either Medicare enrollment, end of the study period, or who died from causes other than BC, were censored at that time and were considered alive.

Healthcare utilization—We examined inpatient visits, emergency department visits, and hospice care, derived from Medicare claims files. To account for differences in follow-up time, we used a log of follow-up years as an offset in the multivariable regressions of healthcare utilization.

Medicare Expenditures—We used the Medicare claims files including inpatient, hospital outpatient, carrier, and durable medical equipment files, to calculate direct all-cause Medicare expenditures. Expenditures were defined as the amounts reimbursed by Medicare to the providers. Expenditures were summed over the follow-up period and an average per month expenditure was calculated based on patient's follow-up months. Expenditures were adjusted to 2019 US dollars to account for differences in currency valuation over time.[25]

Explanatory Variables—We controlled for patient factors including age at cancer diagnosis, year of cancer diagnosis, race, marital status, census tract median household income, and percentage of people age ≥25 years with at least four years of college education. We also controlled for the following clinical characteristics: HR status, HER2 status, tumor grade, comorbidity scores[26–28] derived from co-occurring chronic conditions within 12 months before BC diagnosis, performance status proxies,[29] and the number of sites with cancer metastasis. Based on HR status and HER2 status, we determined tumor status and categorized women as HER2+/HR+, HER2+/HR-, HER2-/HR+, and HER2-/HR-. The SEER file provides information on location of metastasis to lung, liver, brain, and bone, which was used to identify the number of sites with cancer metastasis. Additionally,

for modeling predictors of guideline-concordant treatment and the association between guideline-concordant treatment and survival, we controlled for healthcare use which comprised of medical oncology office visits during the follow-up period.[30] Furthermore, we controlled for location of residence, SEER region, and census level data on number of hospitals offering oncology services.

Statistical Analyses

We described the study cohort using descriptive statistics and used Chi-square tests to determine the significant differences between women who received guideline-concordant treatment vs. those who did not receive guideline-concordant treatment. The proportion of the study cohort which received guideline-concordant care was determined and a multivariable logistic regression was used to identify its significant predictors while controlling for all explanatory variables described above. We then conducted separate multivariable Cox proportional hazards models to examine all-cause and breast cancer-specific mortality by guideline concordance to the cancer treatment. To evaluate the proportional hazards assumption, we plotted the Schoenfeld residuals against time and found no indication of a systematic deviation from proportional hazards. We examined the associations between each component of healthcare utilization and guideline-concordant treatment using multivariable Poisson regressions. We determined corresponding adjusted incidence rate ratios (AIRR) comparing non-guideline-concordant treatment and guideline-concordant treatment. For each Poisson regression, we used a log of follow-up years as an offset to control for differences in follow-up time. Additionally, we used a generalized linear model with log link function and gamma distribution to examine the association between guideline-concordant treatment and average monthly Medicare expenditures, controlling for significant covariates. From the regression, we exponentiated the regression estimates (betas) to obtain the percentage higher or lower monthly Medicare expenditures.

All analyses were two-sided and conducted at 0.05 significance level, using SAS version 9.4 (SAS Institute Inc., Cary, NC). The study was considered exempt from the human subjects research by the University of Rhode Island Institutional Review Board.

RESULTS

Descriptive Characteristics

A total of 1,282 older women diagnosed with *de novo* MBC during 2010–2013 with a median follow-up of 17 months, were included in the study. Most of the cohort was in the age group >75 years (55.6%), white (85.1%), resided in metro areas (83.5%), single, divorced, or widowed (70.8%), had HER2-/HR+ tumor (67.8%), good performance status (73.5%), and at least one comorbidity (60.3%) (Table 1).

Seventy-four percent of women received guideline-concordant initial systemic treatment within six months of cancer diagnosis as per the NCCN treatment guidelines, while 25.8% did not receive guideline-concordant initial systemic treatment. Women receiving guideline-concordant treatment were significantly more likely to be comparatively younger, married/partnered, resided in non-metro areas, and had good performance status. In addition, women

receiving guideline-concordant treatment were less likely to have triple negative tumors or HER2+/HR- tumors than those with HER2+/HR+ tumors. Furthermore, women who were diagnosed with MBC in 2013 were significantly more likely to receive guideline-concordant treatment than those diagnosed during 2010–2012. Among women with MBC who did not receive guideline-concordant initial systemic treatment, 96% had no Medicare claim for recommended treatment regimen per the tumor status within the six months of cancer diagnosis, while four percent received non-recommended initial regimens. This four percent of patients with triple negative tumors received endocrine therapy as an initial therapy while the NCCN guidelines recommend using chemotherapy as an initial therapy.

Predictors of Guideline-Concordant Initial Treatment

Women aged 70 years and older were significantly less likely to receive guideline-concordant initial systemic treatment compared to those aged 66–69 years ($p<0.05$) (Table 2). The adjusted odds ratios (AOR) were 0.594, 0.549, and 0.467 for women in the age groups 70–74, 75–79, and 80 years and above, respectively. Compared to women with HER2+/HR+ tumors, those with HER2+/HR- and HER2-/HR- tumors were significantly less likely to receive guideline-concordant treatment (AOR=0.501, $p=0.0499$ for HER2+/HR- tumors and AOR=0.192, $p<0.0001$ for HER2-/HR- tumors). Women living in non-metro areas (AOR=1.498, 95% confidence interval (CI)=1.004–2.235) and who were married or partnered (AOR=1.632, 95% CI=1.172–2.272) were significantly more likely to receive guideline-concordant treatment. Additionally, women with good performance status were 37% more likely to receive guideline-concordant treatment than women with poor performance status (AOR=1.367, 95% CI=1.013–1.844).

All-Cause and Breast Cancer-Specific Mortality

In the adjusted Cox proportional hazards model, women who did not receive guideline-concordant treatment had significantly higher hazards of dying from any cause (adjusted hazards ratio (AHR)=2.364, 95% CI=2.021–2.766, $p<0.0001$) (Table 3). Similarly, the hazards of dying from breast cancer were higher (AHR=2.179, 95% CI=1.824–2.603, $p<0.0001$) for women who did not receive guideline-concordant treatment compared to those who received guideline-concordant treatment.

Healthcare Utilization and Medicare Expenditures

After controlling for all the covariates, women who did not receive guideline-concordant care had approximately 50% higher rate for both inpatient and emergency room visits compared to women who received guideline-concordant care (AIRR=1.506, 95% CI=1.377–1.648, $p<0.0001$ for inpatient visits, and AIRR=1.502, 95% CI=1.369–1.647, $p<0.0001$ for emergency room visits) (Table 4). Additionally, the odds of hospice use were significantly higher for women with non-guideline-concordant care compared to women who received guideline-concordant care (AOR=6.238, 95% CI=4.528–8.591, $p<0.0001$)

In a multivariable generalized linear regression, adjusted average monthly overall Medicare expenditures for women who did not receive guideline-concordant treatment were significantly higher by 100.4% (95% CI=77.3%−126.5%, $p<0.0001$) compared to those who received guideline-concordant treatment.

DISCUSSION

Several new anticancer therapies that prolong survival of patients with cancer have been developed in recent past years. However, not all patients with cancer receive initial cancer therapies or any initial cancer treatment recommended by the clinical guidelines. We examined a population-based sample of older women diagnosed with de novo MBC during 2010–2013 from the SEER-Medicare database, controlled for a comprehensive list of confounders including performance status and availability of hospitals offering oncology services, and found that one in four women did not receive initial systemic therapy as per the recommended NCCN treatment guidelines. This finding is similar to that reported in a previous study,[12] but marginally lower than that reported in another study.[7] This inconsistency between studies may be due to the difference in the timeframe within which guideline-concordant initial treatment was measured. We examined the initial systemic therapy utilized within the six months of cancer diagnosis similar to the approach adopted by Poorvu et al., while the later study did not use a specific timeframe within which treatments were assessed. In our study, about 50% of women with triple negative tumor subtype MBC and one-fourth of all women with MBC did not receive initial systemic treatment as per the NCCN guidelines, with a majority not receiving any initial treatment within the six months of cancer diagnosis thereby highlighting opportunities for improving initial cancer care in this vulnerable group.

Among older women with MBC, increasing age was associated with a lack of receipt of guideline-concordant initial systemic treatment, a finding consistent with what is previously reported.[12] Advanced cancer therapies including targeted therapy and chemotherapy can cause significant toxicities, particularly among older women.[31] Additionally, patients may choose to forego cancer treatment due to several factors including their older age and patient preferences. However, information on patient preferences was not available in the SEER-Medicare database and therefore they were not assessed. Guideline-concordant treatment is an important metric to assess quality care but given the incurable nature of MBC, it is critical to engage patients in their cancer care decisions and hence examine patient needs, values, and preferences as sources of disparate care in this population. Very few studies have examined patients' role in shared decision making for managing advanced and metastatic cancers. One study focused on understanding the expectations and priorities for symptom management of patients with MBC,[32] while the other study examined the needs and concerns of patients with MBC at disease diagnosis and treatment change.[33] Further research is warranted to examine how patient-centered care that emphasize patient perspectives and preferences, impact guideline-concordant treatment for MBC.

Consistent with published literature,[12,34] we found that women with breast cancer who were married or partnered were more likely to receive initial cancer treatment, suggesting that availability of social support can facilitate receipt of guideline-concordant treatment. Women with poor performance status were less likely to receive guideline-concordant treatment and this suggests that physicians may provide less aggressive cancer treatments or patients may prefer to not receive aggressive cancer treatments (e.g. chemotherapy) owing to their poor performance status. Moreover, women with triple negative or HER2+/HR- MBC were significantly less likely to receive guideline-concordant treatment compared to those with

HER2+/HR+ tumors, which highlighted an area of improvement in breast cancer care. Triple negative tumors have been managed using conventional cytotoxic chemotherapy which causes substantial side effects.[35,36] Due to unavailability of effective cancer therapies with lower toxicity levels for triple negative tumors, women with such tumor subtype may be less prone to choosing to receive guideline-concordant initial therapy. Also, older patients with triple negative tumors who have poor performance status may have difficulty tolerating the conventional cytotoxic chemotherapies thereby contributing to lower adherence to the treatment guidelines as risk-benefit ratio may be difficult to balance. Additionally, women with triple negative or HER2+/HR- tumors have shorter survival with limited benefit from cancer therapy[37] compared to those with HER2+/HR+ tumors, and hence physicians may be less likely to deliver guideline-concordant treatment. For women with HR+ tumors, endocrine therapy is the preferred first-line therapy, which has comparatively lower toxicity, therefore such patients are relatively more likely to receive that guideline-concordant initial treatment. We also found that women who had higher medical oncology office visits were more likely to receive guideline-concordant initial systemic therapy, a finding consistent with that found in the literature. A prior study has shown that women with MBC who have more frequent oncology office visits are likely to receive intensive chemotherapies.[38] Additionally, even though year of cancer diagnosis was a significant predictor of guideline-concordant treatment in the unadjusted regression, we found that it became non-significant in the multivariable analyses.

This is one of the very few studies that have examined the association between guideline-concordant initial treatment and clinical and economic outcomes in women with de novo MBC. Women who received guideline-concordant initial treatment had significantly longer all-cause and breast cancer-specific survival compared to those who did not receive guideline-concordant treatment. This finding only reveals an association. It is possible that improved survival would have been observed with a higher use of guideline-concordant treatment among patients who were older and had more advanced disease. However, the association we observed merely indicates that patients with poorer clinical status were both more likely to die during the study period and to less frequently receive guideline-concordant treatment, which may have been due to patient choice. Future studies using experimental designs that can access patient preferences, severity of comorbidities, and patient's life expectancy, all of which impact receipt of cancer treatment and mortality in patients with MBC, are warranted. One previous US-based study found some survival benefit (15% lower risk of death) for women who received guideline-concordant care, however, the findings were not statistically significant.[7] This inconsistency in the study findings may be partly because this study examined initial systemic therapy within the six months of cancer diagnosis and also due to non-inclusion of several covariates including performance status, number of sites of metastasis, and availability of oncology hospital services in the area of patient's residence, in the regression analyses.

Healthcare resource utilization including inpatient visits, emergency room visits, hospice use, and expenditures to Medicare were significantly higher for women who received non-guideline-concordant initial treatment compared to women who received guideline-concordant treatment. Our findings are partly coherent with other findings reported in the literature for MBC[7,12] and also for early stage breast cancer[39] or other cancer types.[40]

For instance, Poorvu et al. found that inpatient visits were lower among patients who received initial systemic therapy compared to those who did not receive initial systemic therapy.[12] While Rocque et al. found that inpatient visits and emergency room visits were higher among patients who received non-guideline-concordant treatment than those who received guideline concordant treatment, but the differences were not significant.[7] Additionally, our finding about higher expenditures for non-guideline concordant group is similar to that reported earlier.[7] The odds of hospice use were significantly higher for patients who did not receive guideline-concordant treatment compared to those who received guideline-concordant treatment, thereby indicating increased use of palliative care in patients not receiving guideline-concordant treatment. This finding is consistent with other studies, as women with triple negative and HER2+/HR- tumors[37,41] and those who are relatively older,[41] are associated with higher hazards of death.

This study provides insights about the impacts of disparate cancer care in women with *de novo* MBC, but there are few limitations to note. There is no information about severity of comorbidities which may impact cancer treatment selection, however, we controlled for performance status using a claims-based algorithm in the analyses. Additionally, we assessed all-cause healthcare utilization and Medicare expenditures and did not differentiate utilization and expenditures associated with cancer and specific comorbidities. Important information on physician and patient preferences that may impact guideline-concordant treatment is not captured within the database, and hence was not controlled in the analyses. Some patient-level covariates such as annual household income, education level, and access to hospitals offering oncology services are not available in the SEER-Medicare database and hence census tract level information was used.[42] Additionally, the Medicare claims may not capture all the systemic therapies received by the enrollees. This is true for women who may have received treatment due to their enrollment in clinical trials. We examined receipt of initial systemic treatment only, and not the subsequent treatments which may affect patient survival and use of healthcare services. Furthermore, our study findings may not completely reflect the breast cancer treatment patterns in 2020, as several drugs have been approved after 2013 for MBC. Due to the approvals of several newer cancer therapies including HER2-targeted drug like tucatinib, programmed death receptor-1 (PD-1) or its ligand PD-L1 inhibitors like atezolizumab for triple-negative MBC, and the CDK4/6 kinase inhibitors such as palbociclib, ribociclib, and abemaciclib for HR positive cases, the proportion of women receiving guideline-concordant care may be higher in the current population. Additionally, treatment-related expenditures would likely be higher due to the increased cost of newer regimens. We did not adjust for the expected increase in healthcare utilization and Medicare expenditures at the end of life for patients who died during the follow-up period. However, we examined the Medicare costs for the last month of life for patients who died. The average Medicare costs in the last month of life for patients who received guideline-concordant treatment and those who did not receive guideline-concordant treatment were not statistically different, and the average amount was only marginally higher than that reported for the overall guideline-concordant cohort. Lastly, this study included older patients enrolled in Medicare fee-for-service program and therefore these findings are not generalized to younger women and those enrolled in commercial insurance plans.

CONCLUSION

One-fourth of older women with *de novo* MBC did not receive guideline-concordant initial systemic treatment, especially among those with triple negative tumors. All-cause and breast cancer-specific mortality, healthcare utilization, and Medicare expenditures were higher for women who did not receive guideline-concordant initial cancer care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of Medicare FFS Beneficiaries with Metastatic Breast Cancer By Receipt of Guideline-Concordant Initial Treatment SEER-Medicare 2010–2013 Cases

	Total cohort		Guideline-concordant Treatment		Non Guideline-Concordant Treatment		p-value
Variables	**N = 1,282**	**%**	**n = 951 (74.2%)**	**%**	**n = 331 (25.8%)**	**%**	
Age at Diagnosis							<0.0001
66–69	242	18.8%	204	84.3%	38	15.7%	
70–74	324	25.3%	250	77.2%	74	22.8%	
75–79	281	21.9%	209	74.4%	72	25.6%	
80,+	435	33.9%	288	66.2%	147	33.8%	
Race/Ethnicity							0.630
Whites	1091	85.1%	812	74.4%	279	25.8%	
Other	191	14.9%	139	72.7%	52	27.2%	
Marital Status							<0.0001
Married/Partnered	375	29.3%	306	81.6%	69	18.4%	
Single/Divorced/Widowed	907	70.7%	645	71.1%	262	28.9%	
Location of Residence							0.032
Metro	1071	83.5%	782	73.0%	289	27.0%	
Non-metro	211	16.5%	169	80.1%	42	19.9%	
SEER Region							0.119
North East	317	24.7%	226	71.3%	91	28.7%	
South	334	26.1%	254	76.1%	80	23.9%	
North Central	190	14.8%	132	69.5%	58	30.5%	
West	441	34.4%	339	76.9%	102	23.3%	
Census Tract Household Income							0.813
LE $50,000	428	33.4%	322	75.2%	106	24.8%	
$50,001-$75,000	576	44.9%	423	73.4%	153	26.6%	
GT $75,000	278	21.7%	206	74.1%	72	25.9%	
Census Tract Education							0.694
LE 21.5	317	24.7%	240	75.7%	77	24.3%	
21.6–30.2	315	24.6%	227	72.1%	88	27.9%	
30.3–36.1	317	24.7%	233	73.5%	84	26.5%	
GT 36.1	333	26.0%	251	75.4%	82	24.6%	
Tumor Status							<0.0001
HER2+/HR+	154	12.0%	126	81.8%	28	18.2%	
HER2+/HR-	80	6.2%	58	72.5%	22	27.5%	
HER2-/HR+	869	67.8%	677	77.9%	192	22.1%	
HER2-/HR-	179	14.0%	90	50.3%	89	49.7%	
Grade of Tumor							0.042
Well/Moderately differentiated	539	42.0%	417	77.4%	122	22.6%	

Variables	Total cohort N = 1,282	%	Guideline-concordant Treatment n = 951 (74.2%)	%	Non Guideline-Concordant Treatment n = 331 (25.8%)	%	p-value
Poorly/Un-differentiated	470	36.7%	331	70.4%	139	29.6%	
Unknown	273	21.3%	203	74.4%	70	25.6%	
Number of Metastatic Sites[§]							0.829
0–1	912	71.1%	675	74.0%	44	26.0%	
2–4	370	28.9%	276	74.6%	12	25.4%	
Performance Status							0.0008
Good	942	73.5%	722	76.7%	220	23.3%	
Poor	340	26.5%	229	67.4%	111	32.6%	
Comorbidity							0.047
0	509	39.7%	390	76.6%	119	23.4%	
1	288	22.5%	220	76.4%	68	23.6%	
2,+	485	37.8%	341	70.3%	144	29.7%	
Oncology Visits							<0.0001
0–8	420	32.8%	245	58.3%	175	41.7%	
9–30	422	32.9%	311	73.7%	111	26.3%	
31,+	440	34.3%	395	89.8%	45	10.2%	
Hospitals Offering Oncology Services							0.337
0–1	448	35.0%	343	76.6%	105	23.4%	
2–5	486	37.9%	352	72.4%	134	27.6%	
6,+	348	27.2%	256	73.6%	92	26.4%	
Year of Cancer Diagnosis							0.024
2010	264	20.6%	189	71.6%	75	28.4%	
2011	299	23.3%	214	71.6%	85	28.4%	
2012	344	26.8%	248	72.1%	96	27.9%	
2013	375	29.3%	300	80.0%	75	20.0%	

HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormone Receptor; AOR: Adjusted Odds Ratio; CI: Confidence Interval; FFS: Fee-for-service; LE: Less than; GT: Greater than

Table 2

Adjusted Odds Ratios of Receiving Guideline-Concordant Initial Treatment Among Medicare FFS Beneficiaries with Metastatic Breast Cancer SEER-Medicare 2010–2013 Cases

Variables	Guideline-Concordant Treatment		
	AOR	95% CI	p-value
Age at Diagnosis			
66–69	**Reference**		
70–74	0.594	[0.372, 0.947]	0.0285
75–79	0.549	[0.342, 0.879]	0.0126
80,+	0.467	[0.303, 0.720]	0.0006
Race/Ethnicity			
White	**Reference**		
Other	1.426	[0.960, 2.116]	0.0786
Location of Residence			
Metro	**Reference**		
Non-metro	1.498	[1.004, 2.235]	0.0477
Marital Status			
Married/Partnered	1.632	[1.172, 2.272]	0.0038
Single/Divorced/Widowed	**Reference**		
Tumor Status			
HER2+/HR+	**Reference**		
HER2+/HR-	0.501	[0.260, 1.000]	0.0499
HER2-/HR+	0.769	[0.494, 1.255]	0.3179
HER2-/HR-	0.192	[0.111, 0.330]	<0.0001
Performance Status			
Good	1.367	[1.013, 1.844]	0.0410
Poor	**Reference**		
Oncology Visits			
0–8	**Reference**		
9–30	1.930	[1.420, 2.623]	<0.0001
31,+	6.173	[4.202, 9.072]	<0.0001

HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormone Receptor; AOR: Adjusted Odds Ratio; CI: Confidence Interval; FFS: Fee-for-service

Table 3

Adjusted Hazards Ratios* for All-Cause and Breast-Cancer Specific Mortality Among Medicare FFS Beneficiaries with Metastatic Breast Cancer SEER-Medicare 2010–2013 Cases

	Non Guideline-Concordant Initial Treatment		
	AHR	**95% CI**	**p-value**
All-Cause Mortality			
Guideline-Concordant			
Initial Treatment	**Reference**		
Non-Guideline Concordant			
Initial Treatment	2.364	[2.021, 2.766]	<0.0001
Breast Cancer-Specific Mortality			
Guideline-Concordant			
Initial Treatment	**Reference**		
Non-Guideline Concordant			
Initial Treatment	2.179	[1.824, 2.603]	<0.0001

*Adjusted for age at cancer diagnosis, race/ethnicity, marital status, census level household annual income and education level, location of residence, grade of tumor, comorbidity, performance status, tumor status, number of sites with metastasis, number of hospitals offering oncology services in area of patient's residence, number of oncology visits

AHR: Adjusted Hazards Ratio, CI: Confidence Interval

Table 4

Healthcare Resource Utilization and Medicare Expenditures Among Medicare FFS Beneficiaries with Metastatic Breast Cancer Without Guideline-Concordant Initial Treatment SEER-Medicare 2010–2013 Cases

	Non Guideline-Concordant Initial Treatment*		
Any Healthcare Utilization*	**AOR**	**95% CI**	**p-value**
Any Inpatient Use	6.024	[3.936, 9.270]	<0.0001
Any Emergency Room Visit	4.335	[2.884, 6.516]	<0.0001
Any Hospice Use	6.238	[4.528, 8.591]	<0.0001
Healthcare Utilization*	**AIRR**	**95% CI**	**p-value**
Number of Inpatient Visits	1.506	[1.377, 1.648]	<0.0001
Number of Emergency Room Visits	1.502	[1.369, 1.647]	<0.0001
Average Monthly Medicare Expenditures**	**Adjusted Beta-Coefficients**	**95% CI**	**% Higher Expenditures**
Intercept	8.7319§	[8.5284, 8.9353]	
Non Guideline-Concordant Initial Treatment	0.6953***	[0.5728, 0.8177]	100.4%

*As compared with guideline-concordant initial treatment; adjusted for age at cancer diagnosis, race/ethnicity, marital status, census level annual household income and education, location of residence, SEER region, grade of tumor, comorbidity, performance status, tumor status, number of sites with metastasis, number of hospitals offering oncology services in the area of patient's residence

**Adjusted for variables that were significant in the backward selection: census level household annual income (reference="greater than $75,000") and education level (reference="Greater than 36.1"), SEER region (reference="Northeast"), comorbidity (reference="0"), tumor status (reference="HER2-/HR+"), number of sites with metastasis (reference="2–4"), number of hospitals offering oncology services in area of patient's residence (reference=0–1")

§The beta coefficient represent the mean estimate with other covariates fixed at their reference categories listed above.

***p<0.0001

AOR: Adjusted Odds Ratio, AIRR: Adjusted Incidence Rate Ratio; CI: Confidence Interval