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Surgery and Survival in Patients with Stage IV Breast Cancer

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Abstract

Background: Retrospective studies have shown some improvement in survival for patients receiving surgical management of the intact primary tumor in patients with presenting with Stage IV disease, while prospective studies have revealed mixed results.

Methods: An examination of the NCDB from 2004–2013 was undertaken to examine factors related to the utilization of surgery and overall survival in patients with de novo Stage IV disease. Univariate and multivariable analyses were conducted to determine factors related to survival. Propensity score matching method was implemented to balance patients' baseline characteristics.

Results: A total of 11,694 patients with Stage IV breast cancer at diagnosis met inclusion criteria. Surgical intervention occurred in 5,202 patients (44.5%), with the use of surgery decreasing throughout the study period (53.6% surgery 2004–2006; 31.8% surgery 2011–2013). Selection for surgical intervention was associated with small tumors (T1) and a higher nodal burden (N2/3). Uninsured patients, those treated at academic centers, those treated in the Northeast, and those with hormone receptor positive tumors were less likely to undergo surgery. Surgery was independently associated with a better overall survival. Propensity score matching revealed a persistent survival advantage for surgical patients receiving surgery, regardless of the receipt of systemic therapy.

Conclusions: Surgery on the intact primary tumor for patients presenting with de novo Stage IV breast cancer is associated with improved overall survival. Surgical resection in patients with Stage IV breast cancer should be considered for well-selected patients as a part of multimodality therapy.

BACKGROUND

Breast cancer is the most common cancer among women in the United States, with 252,710 cases of invasive cancer expected in 2017, 6% of whom will present with de novo Stage IV disease.[1, 2] Survival for these patients has steadily improving over the last several decades.[3, 4] Ruiterkamp et al., noted median overall survival in de novo Stage IV breast cancer increased from 1.42 years (1995–1999) to 1.95 years (200o5–2008).[4] Targeted agents and recent improvements in systemic therapy allow many patients to live longer lives, often with

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no obvious evidence of disease other than the intact primary tumor.[2, 3, 5] These improvements in systemic therapies, and even improved Hospice care approaches, are encouraging clinicians to consider local disease management as an option in patients with de novo stage IV disease.

There has been continued interest in the utility of surgical resection of the primary tumor in de novo metastatic breast cancer, possibly increasing survival rather than just providing palliation. Multiple retrospective studies have noted a survival advantage for de novo stage IV breast cancer patients undergoing surgical resection of the primary tumor.[6–8] Small, prospective, randomized trials, have revealed mixed results without a definitive answer.[9, 10] Thus most guidelines still recommend against surgical intervention except in palliative situations. Clinicians, when faced with a patient with limited metastasis and a resectable primary tumor, are often challenged to determine the true utility of surgical resection within the context of modern multimodality treatment. This study attempts to undertake a modern, robust examination of the National Cancer Data Base (NCDB) to examine of the utility of surgical locoregional disease control in patients with de novo stage IV breast cancer in the current clinical setting.

METHODS

Patient Population

This study used the most recent 2014 Participant User File (PUF) for patients with a diagnosis of breast cancer from 2004–2013. The study population was defined as all female patients aged >=40 with pathologically proven Stage IV invasive breast cancer at time of diagnosis, excluding patients with recurrent, metastatic breast cancer. Patients with an incomplete record related to outcome measures, a non-invasive cancer diagnosis, occult primary tumor, planned palliative treatment or only a biopsy/diagnostic surgical procedure were excluded. Definitive surgery was defined as non-palliative lumpectomy (partial mastectomy) or mastectomy.

Outcome

Overall survival (OS) is the primary clinical outcome, was defined as months from date of diagnosis to date of death or date of last follow up if alive.

Statistical Analysis

Statistical analysis was conducted using SAS Version 9.4, and SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Insititute.[11] The univariate association of each covariate with cohorts was assessed using the chi-square test for categorical covariates and ANOVA for numerical covariates. A multivariable logistic regression model was fitted to predict the utilization of surgery. The association with overall survival was modeled by the extended Cox proportional hazards model to handle the potential guarantee-time bias in which patients were held in the non-surgical group initially and switched to the surgical group when he/she had the surgery.[12] An extended Kaplan-Meier estimator was generated accordingly. All multivariable models were built by a backward variable selection procedure with an alpha = 0.2 removal criteria. The subgroup

analysis was carried out in the multivariable model including interaction term between study cohorts and a stratified variable. In addition, patients from the surgical group were matched to the one from the non-surgery group through non-replacement 1:1 matching with caliper as 0.2 standard deviation of logit of propensity score (PS). The balance of covariate between cohorts after PS matching was evaluated by the standardized differences and a value of < 0.1 was considered as negligible imbalance.[13] The comparison of overall survival was estimated in the matched sample by an extended Cox model with a robust variance estimator.[14]

RESULTS

Description of the Cohort

There were 11,694 patients with de novo Stage IV breast cancer who meet the inclusion criteria for the study period 2004–2013, median age was 61 (Table1). The number of patients with de novo Stage IV breast cancer undergoing definitive surgical therapy decreased throughout the study period from 53.6% (2004–2006) to 31.8% (2011–2013) (Table 2).

Factors Influencing Surgery

5,202 patients (44.5%) underwent definitive surgery, while 6,492 patients did not (55.5%). On univariate analysis, younger age, Caucasian race, private insurance, and treatment at a community cancer program were all associated with receiving surgical intervention (Table 2). Multivariable analysis of non-clinical factors revealed that patients who received surgery were more likely to be treated at a community cancer program, in the South, or had private insurance. There was a clear trend of decreased surgical intervention during the study period. Multivariable analysis of clinical factors revealed that patients with T1 tumors and higher nodal status were the most likely to receive surgical intervention (Table 2).

Factors Influencing Survival

Surgical intervention was associated with an improvement in OS (HR 0.82 [0.78–0.87], p<0.001). An improved OS was associated with higher income level, private insurance, and well-differentiated, T1 tumors (Table 3). African American patients, patients with a higher Charlson-Deyo score and those treated outside of an academic/research program all had a decreased OS. Failure to receive systemic therapy or radiation therapy was also associated with decreased OS (Table 3).

When selectively examining patients undergoing surgery, there was a persistent association with increased OS for Caucasian (in comparison to African American) patients, patients with private insurance, those with higher associated median income, as well as those with hormone receptor positive tumors. Lack of systemic therapy or radiation therapy, as well as treatment at a community cancer program, was also associated with a poorer OS in the surgical group (Table 4). A positive resection margin in patients undergoing surgical resection of their primary tumor was associated with a markedly decreased OS (HR 1.38, [1.27–1.50], p<0.001) (Table 4).

Overall Survival

For de novo metastatic disease, patients undergoing surgical intervention had a median OS of 51.8 months compared to 38.1 months for the non-surgical group (p<0.001). Patients undergoing breast conservation surgery were noted to have increased OS when compared with mastectomy (54.8 months versus 47.6 months, p=0<001). When systemic therapy is added to the analysis, patients undergoing both surgery and systemic therapy had the longest median OS at 54.8 months while patients receiving no intervention have only 19.4 month median OS (p<0.001). Multivariable association with OS revealed a persistent improvement in survival with surgery either with (HR 0.87 [0.82–0.93], p<0.001) or without the addition of systemic therapy (HR 0.61 [0.55–0.69], p<0.001). Propensity score matched analysis also displayed a significant association with improved OS for patients undergoing surgical therapy, regardless of the receipt of systemic therapy (HR 0.68 [0.63–0.72], p<0.001)(Table 5).

DISCUSSION

This updated analysis of a modern cohort of 11,694 patients from the NCDB with de novo Stage IV breast cancer sheds additional light on the possible benefits of surgical intervention for these patients. Analysis reveals that well-selected patients may enjoy an improvement in overall survival with definitive, margin negative, surgery for their primary disease as a part of multimodality care. This survival advantage of surgery persisted over time despite decreasing utilization of surgery during the study period, obvious improvements in systemic therapy, and isolation of potentially confounding factors with propensity score matching.

The question of the utility of surgical resection of the primary tumor in this patient population has been long debated. Multiple retrospective studies have pointed to the potential benefit to surgery.[7, 15–22] Khan, et al., in the first examination of the NCBD (1990–1993), noted that there was a survival advantage for the surgery group (HR 0.61, 95% CI 0.58–0.65) with a need to reassess the role of surgery in this patient population.[20] Two recent meta-analyses also noted a survival advantage for patients undergoing surgical resection as a part of their disease management.[7, 8] The most recent examination of the SEER database (1988–2011) again proposed a benefit to surgical intervention in patients with Stage IV breast cancer. In an examination of a sample of 21,372 cases, an improved overall survival for the surgical group was noted when compared to the non-surgical group (HR 0.60, 95% 0.57–0.63).[23] These findings are confirmed in this analysis of the NCDB, providing consistent evidence based on observational data that well selected patients with de novo Stage IV breast cancer who undergo surgical resection of their primary tumor enjoy significantly improved survival, despite the clinical dogma suggesting otherwise.

Despite the results of multiple retrospective analyses supporting a survival benefit to surgery in this patient population, there was always a lack of supportive prospective analyses. Badwe et al., performed a randomized controlled trial (350 patients), examining the response to systemic therapy in patients with de novo Stage IV breast cancer and then randomizing to surgery or no surgery of an intact primary.[9] They found no difference in overall survival based on local disease management. Soran et al., randomized 274 patients with metastatic disease at diagnosis to either local regional therapy or systemic therapy.[6] Survival was

similar at 36 months, but actually higher in the surgical group versus the systemic therapy alone group at 60 months (42% versus 25%). They specifically noted that patients with a higher metastatic burden had a lower survival while patients with more favorable tumor histology did better. In the United States, The Translational Breast Cancer Research Consortium performed a prospective registry study, treating a cohort of patients with metastatic breast cancer with systemic chemotherapy and then offered surgical intervention to patients who were deemed therapy responders.[10] This study of 127 patients noted no improvement in overall survival for those having resection of their intact primary disease despite an admitted selection bias for the surgery group. Subset analysis failed to identify a group that benefited from surgery, albeit the groups were markedly limited in size.[10] Thus, prospective trials failed to provide a definitive answer to the question of optimal utility of surgery in this patient population. Although we await the results of other trials examining this issue, it is difficult to completely ignore the plethora of results from retrospective studies indicating a benefit of surgical intervention in this patient population.

The current examination of the NCDB provides strong retrospective data driven support of surgical extirpation of the intact primary tumor. But there are a number of key limitations that require examination prior to extoling the benefits of surgical therapy in this population. Selection bias and stage migration are recognized issues in retrospective analyses.[17] Multiple studies have confirmed that Stage IV breast cancer patients undergoing resection of their intact primary tumor are often younger, have smaller tumors, and have less of a metastatic burden. [23–25] Bafford et al., noted that patients diagnosed with metastatic disease prior to surgical intervention had survival rates very similar to patients receiving no surgery at all (2.36 years versus 2.4 years), while patients diagnosed postoperatively had a notable increase in survival (4 years).[16] Often, patients presenting with a presumed lower burden of disease are not subjected to whole body imaging. Thus, surgical staging of the axilla may upstage patients with presumed Stage I or II disease.[26] A review of the utility of surgery in Stage IV breast cancer patients noted that approximately 20% of patients receive surgery for palliative purposes, 22% have surgery for local control (true extirpation of the primary tumor as a part of treatment plan), and 28–49% receive surgery prior to their definitive diagnosis of metastatic disease.[18, 21, 27] In a matched paired analysis, researchers noted that selection bias in the form of misclassification of either stage or surgical procedure can affect findings.[18] But, it could be argued that patient's without obvious signs of metastatic disease are the ideal candidates for surgical excision of their primary tumor. The survival benefit amongst patients in the major retrospective studies cited is similar, suggesting a similar level of bias exhibited by clinicians when choosing surgical candidates. The issues of selection bias and stage migration are issues that we attempted to at least partially control through propensity score matching. The results of propensity score matching in this study supported the benefit of surgical intervention in terms of OS more significantly than other analyses (HR 0.68, 95% 0.63–0.72, $p<0.001$). Although not to the level of a randomized, controlled trial, this statistical analysis notes an improvement in OS that closely resembles those noted by multiple previous large database driven studies and meta-analyses (HR 0.60–0.68).[7, 8, 20, 22, 23]

Another key limitation of this study is the outcome of overall survival versus cancer-specific survival. The NCDB only includes vital status with death from any cause. However, in the

metastatic setting, this limitation may be less important as it may be that most women will die from advanced breast cancer rather than other co-morbid conditions or additional causes of death. But when comparing outcomes from different data sources, the type of primary outcome measure should be a consideration.

Surgical resection of the intact primary tumor provides a clear survival benefit in patients with stage IV breast cancer in this study sample. The actual selection of patients that will gain a benefit remains the main challenge facing clinicians in light of conflicting retrospective and prospective data. When examining de novo Stage IV patients, the current survival is in the range of 27 to 29 months.[28, 29] Survival is notably higher for hormone receptor positive disease (34 months) and HER2 positive disease (29 months) when compared with triple negative breast cancer (11 months). These results are in line with the findings of this study. Identifying patients who may live long enough for the primary tumor to become a symptomatic issue or patients in whom the primary tumor may be the only obvious site of disease after systemic therapy would greatly aid in decision making. Based on our data, it appears that patients with well-differentiated tumors, a lower burden of disease at presentation (T1), hormone receptor positive, and the ability to provide a margin negative resection may be factors that help identify those who would benefit most from surgical intervention. It is also clear that the receipt of systemic therapy is essential. The overall survival for patients receiving systemic therapy and surgery was 56.8 months, but only 29.8 months for those receiving surgery alone.

Breast cancer outcomes continue to improve, including for patients presenting with metastatic disease. In this modern analysis of patients presenting with stage IV breast cancer, surgical resection of their intact primary tumor was associated with an improved overall survival. Systemic therapy is of clear importance, often providing a larger contribution to overall survival than local therapies. Patients treated with a multimodality approach will experience the longest overall survival in comparison to those treated with single therapies. An individualized multimodality treatment approach should be applied to each patient presenting with de novo stage IV breast cancer and an intact primary tumor.

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Table 1:

Selection/Exclusion Diagram

Selection and Exclusion Criteria	Sample Size	Excluded
NCDB Breast PUF Cancer Cases	2246280	-
Year of diagnosis 2004 ~ 2013	2013437	232843
Exclude BEHAVIOR in situ	1603159	410278
Include sequence number in 0 or 1	1345207	257952
Include Pathological Stage IV with pM1 (exclude T = 0)	20493	1324714
Exclude Patients who got Palliative Care	17020	3473
Exclude male patients	16759	261
Include eligible surgery at primary site	12585	4174
Exclude missing outcome	12509	76
Include patients age >= 40	11694	815

Table 2:

Patient Characteristics and Factors Favoring Surgery

		All Stage IV Patients	Patients Receiving Surgery	Factors Favoring Surgery (Multivariable Analysis)		
Variable		**N = 11694 (%)**	**N = 5202 (%)**	**Odds Ratio (95% CI)**	**P value**	**Type 3 P value**
Age at Diagnosis	Median	61.00	60.00	NS	NS	NS
Race	Caucasian	9461 (80.9)	4285 (45.29)	1.14 (1.00–1.30)	0.052	0.150
	African American	1722 (14.7)	702 (40.77)	1.14 (0.89–1.47)	0.305	
	Other	511 (4.4)	215 (42.07)	-	-	
Charlson-Deyo Score	0	9455 (80.9)	4268 (45.14)	NS	NS	NS
	1	1704 (14.6)	743 (43.6)			
	2+	535 (4.6)	191 (35.7)			
Facility Type	Community Cancer Program/Other	1516 (13.0)	766 (50.53)	1.98 (1.70–2.30)	<.001	<.001
	Comprehensive Community Cancer Program	5268 (45.0)	2488 (47.23)	1.50 (1.34–1.67)	<.001	
	Integrated Network Cancer Program	1073 (9.2)	510 (47.53)	1.45 (1.22–1.72)	<.001	
	Academic/Research Program	3837 (32.8)	1438 (37.48)	-	-	
Facility Location	West	1785 (15.3)	810 (45.38)	1.25 (1.07–1.46)	0.004	<.001
	Midwest	2976 (25.4)	1341 (45.06)	1.17 (1.03–1.34)	0.017	
	South	4163 (35.6)	1984 (47.66)	1.48 (1.31–1.68)	<.001	
	Northeast	2770 (23.7)	1067 (38.52)	-	-	
Primary Payor	Medicare	4405 (37.7)	1843 (41.84)	1.62 (1.34–1.95)	<.001	<.001
	Medicaid/Other Govt	1189 (10.2)	477 (40.12)	1.23 (0.99–1.54)	0.065	
	Private	5214 (44.6)	2603 (49.92)	1.80 (1.49–2.17)	<.001	
	Not Insured/Unknown	886 (7.6)	279 (31.49)	-	-	
Median Income Quartiles (2000)	<$30,000	1615 (14.4)	737 (45.63)	NS	NS	NS
	$30,000 - $35,999	1920 (17.1)	840 (43.75)			
	$36,000-$45,999	3090 (27.5)	1383 (44.76)			

		All Stage IV Patients	Patients Receiving Surgery	Factors Favoring Surgery (Multivariable Analysis)		
Variable		**N = 11694 (%)**	**N = 5202 (%)**	**Odds Ratio (95% CI)**	**P value**	**Type 3 P value**
	$46,000+	4592 (40.9)	2038 (44.38)			
Diagnosis Year	>=2004, <=2006	3513 (30.0)	1882 (53.57)	3.83 (3.34–4.40)	<.001	<.001
	>2006, <=2008	2380 (20.4)	1164 (48.91)	2.56 (2.21–2.96)	<.001	
	>2008, <=2011	3460 (29.6)	1411 (40.78)	1.55 (1.36–1.76)	<.001	
	>2011, <=2013	2341 (20.0)	745 (31.82)	-	-	
Grade	Well Differentiated	684 (5.8)	370 (54.09)	3.78 (3.07–4.66)	<.001	<.001
	Moderately Differentiated	3415 (29.2)	1773 (51.92)	3.62 (3.15–4.16)	<.001	
	Poorly Differentiated/Undifferentiated	4448 (38.0)	2598 (58.41)	4.84 (4.22–5.55)	<.001	
	Cell Type Not Determined	3147 (26.9)	461 (14.65)	-	-	
Analytic T Stage	T1	2025 (17.3)	1094 (54.02)	7.64 (5.95–9.82)	<.001	<.001
	T2	3372 (28.8)	2129 (63.14)	6.08 (4.84–7.63)	<.001	
	T3	1319 (11.3)	693 (52.54)	4.01 (3.13–5.13)	<.001	
	T4	2801 (24.0)	1137 (40.59)	3.11 (2.52–3.85)	<.001	
	Unknown	2177 (18.6)	149 (6.84)	-	-	
Analytic N Stage	No	2690 (23.0)	1272 (47.29)	1.50 (1.30–1.73)	<.001	<.001
	N1	3461 (29.6)	1573 (45.45)	1.45 (1.27–1.66)	<.001	
	N2	956 (8.2)	717 (75)	4.77 (3.90–5.82)	<.001	
	N3	1368 (11.7)	865 (63.23)	3.17 (2.68–3.75)	<.001	
	Unknown	3219 (27.5)	775 (24.08)	-	-	
ER	Negative	2670 (22.8)	1366 (51.16)	1.18 (1.02–1.36)	0.025	<.001
	Positive	7882 (67.4)	3611 (45.81)	1.11 (0.74–1.68)	0.617	
	Unknown	1142 (9.8)	225 (19.7)	-	-	
PR	Negative	4123 (35.3)	2006 (48.65)	0.93 (0.82–1.06)	0.258	<.001
	Positive	6233 (53.3)	2936 (47.1)	0.55 (0.38–0.81)	0.002	
	Unknown	1338 (11.4)	260 (19.43)	-	-	

		All Stage IV Patients	Patients Receiving Surgery	Factors Favoring Surgery (Multivariable Analysis)		
Variable		**N = 11694 (%)**	**N = 5202 (%)**	**Odds Ratio (95% CI)**	**P value**	**Type 3 P value**
Chemotherapy	No	5182 (44.3)	1886 (36.4)	NS	NS	NS
	Yes	6145 (52.5)	3159 (51.41)			
	Unknown	367 (3.1)	157 (42.78)			
Hormone Therapy	No	5775 (49.4)	2425 (41.99)	NS	NS	NS
	Yes	5508 (47.1)	2593 (47.08)			
	Unknown	411 (3.5)	184 (44.77)			
Systemic Therapy	Yes	9470 (81.0)	4509 (47.61)	1.29 (1.13–1.48)	<.001	<.001
	Unknown	105 (0.9)	42 (40)	1.61 (0.96–2.72)	0.073	
	No	2119 (18.1)	651 (30.72)	-	-	
Radiation Therapy	Yes	3510 (30.0)	3076 (38.38)	2.21 (2.00–2.45)	<.001	<.001
	Unknown	169 (1.4)	79 (46.75)	1.63 (1.09–2.43)	0.018	
	No	8015 (68.5)	2047 (58.32)	-	-	
Tumor Size	>2, <=4	2124 (18.2)	1299 (61.16)	1.84 (1.49–2.27)	<.001	<.001
	>4, <=6	2234 (19.1)	1259 (56.36)	1.59 (1.30–1.95)	<.001	
	>6, <=99	2173 (18.6)	1146 (52.74)	1.72 (1.39–2.12)	<.001	
	Unknown	2778 (23.8)	366 (13.17)	0.47 (0.38–0.58)	<.001	
	>=0, <=2	2385 (20.4)	1132 (47.46)	-	-	

Table 3:

Multivariable Association with Overall Survival

		Hazard Ratio (95% CI)	HR p-value	Type3 p-value
Surgery at Primary Site	Yes [n=5202 (44.5%)]	0.82 (0.78–0.87)	**<.001**	**<.001**
	No [n=6492 (55.5%)]	-	-	
Age at Diagnosis		1.01 (1.01–1.02)	**<.001**	**<.001**
Race	Black	1.14 (1.07–1.22)	**<.001**	**<.001**
	Other/Unknown	0.93 (0.83–1.05)	0.260	
	White	-	-	
Charlson-Deyo Score	2+	1.84 (1.66–2.03)	**<.001**	**<.001**
	1	1.27 (1.19–1.35)	**<.001**	
	0	-	-	
Facility Type	Community Cancer Program/Other	1.24 (1.15–1.33)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	1.14 (1.08–1.20)	**<.001**	
	Integrated Network Cancer Program	1.06 (0.97–1.16)	0.179	
	Academic/Research Program	-	-	
Facility Location	Northeast	0.98 (0.91–1.06)	0.606	**0.037**
	South	0.97 (0.91–1.05)	0.482	
	Midwest	1.06 (0.98–1.14)	0.146	
	West	-	-	
Primary Payor	Not Insured/Unknown	1.20 (1.09–1.31)	**<.001**	**<.001**
	Medicaid/Other Government	1.27 (1.18–1.38)	**<.001**	
	Medicare	1.11 (1.04–1.19)	**0.002**	
	Private	-	-	
Median Income Quartiles 2000	< $30,000	1.14 (1.06–1.22)	**<.001**	**<.001**
	$30,000 - $35,999	1.22 (1.14–1.30)	**<.001**	
	$36,000 - $45,999	1.07 (1.01–1.13)	**0.024**	
	$46,000 +	-	-	
Grade	Cell Type Not Determined	1.30 (1.16–1.45)	**<.001**	**<.001**
	Poorly Differentiated/ Undifferentiated	1.36 (1.22–1.51)	**<.001**	
	Moderately Differentiated	1.12 (1.00–1.25)	**0.048**	
	Well Differentiated	-	-	
Analytic T Stage	Unknown	1.13 (1.01–1.25)	**0.028**	**<.001**
	T4	1.33 (1.20–1.47)	**<.001**	
	T3	1.09 (0.97–1.24)	0.151	
	T2	1.04 (0.93–1.16)	0.452	
	T1	-	-	

		Hazard Ratio (95% CI)	HR p-value	Type3 p-value
Analytic N Stage	Unknown	1.17 (1.10–1.26)	**<.001**	**<.001**
	N3	1.07 (0.99–1.16)	0.096	
	N2	0.98 (0.89–1.08)	0.728	
	N1	0.98 (0.92–1.05)	0.617	
	N0	-	-	
ER	Negative	1.31 (1.22–1.41)	**<.001**	**<.001**
	Unknown	1.18 (1.00–1.38)	**0.044**	
	Positive	-	-	
PR	Negative	1.32 (1.24–1.41)	**<.001**	**<.001**
	Unknown	1.12 (0.96–1.31)	0.137	
	Positive	-	-	
Systemic Therapy	No	2.05 (1.93–2.17)	**<.001**	**<.001**
	Unknown	0.93 (0.72–1.21)	0.593	
	Yes	-	-	
Radiation Therapy at any CoC Facility	No	1.19 (1.13–1.25)	**<.001**	**<.001**
	Unknown	0.63 (0.51–0.79)	**<.001**	
	Yes	-	-	

*Number of observations in the original data set = 16183. Number of observations used = 15544.

**Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Percent No High School Degree Quartiles 2000, and Diagnosis Year (quartile).

Table 4:

Multivariable Association with Overall Survival Among Surgery Patients

Covariate	Level	Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Surgery	Mastectomy	0.97 (0.90–1.05)	0.450	0.450
	Breast Conserving Surgery	-	-	
Age at Diagnosis		1.01 (1.01–1.02)	**<.001**	**<.001**
Race	African American	1.11 (1.00–1.24)	**0.049**	0.074
	Other/Unknown	0.91 (0.75–1.10)	0.320	
	Caucasian	-	-	
Charlson-Deyo Score	2+	1.83 (1.53–2.18)	**<.001**	**<.001**
	1	1.24 (1.13–1.37)	**<.001**	
	0	-	-	
Facility Type	Community Cancer Program/Other	1.31 (1.17–1.46)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	1.15 (1.05–1.25)	**0.002**	
	Integrated Network Cancer Program	1.12 (0.98–1.29)	0.093	
	Academic/Research Program	-	-	
Facility Location	Northeast	1.07 (0.95–1.21)	0.268	0.114
	South	1.09 (0.97–1.22)	0.146	
	Midwest	1.15 (1.03–1.29)	**0.017**	
	West	-	-	
Primary Payor	Not Insured/Unknown	1.21 (1.03–1.42)	**0.021**	**0.007**
	Medicaid/Other Government	1.20 (1.06–1.37)	**0.005**	
	Medicare	1.10 (0.99–1.22)	0.076	
	Private	-	-	
Median Income Quartiles 2000	< $30,000	1.08 (0.97–1.21)	0.172	**<.001**
	$30,000 - $35,999	1.30 (1.17–1.44)	**<.001**	
	$36,000 - $45,999	1.13 (1.04–1.24)	**0.005**	
	$46,000 +	-	-	
Grade	Cell Type Not Determined	1.28 (1.06–1.55)	**0.010**	**<.001**
	Poorly Differentiated/Undifferentiated	1.56 (1.33–1.82)	**<.001**	
	Moderately Differentiated	1.20 (1.02–1.40)	**0.025**	
	Well Differentiated	-	-	
Analytic T Stage	Unknown	1.07 (0.83–1.39)	0.600	**<.001**
	T4	1.37 (1.16–1.62)	**<.001**	
	T3	1.09 (0.90–1.31)	0.395	
	T2	1.05 (0.89–1.25)	0.557	
	T1	-	-	

Covariate	Level	Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Analytic N Stage	Unknown	1.34 (1.20–1.50)	**<.001**	**<.001**
	N3	1.16 (1.03–1.29)	**0.011**	
	N2	1.02 (0.90–1.15)	0.757	
	N1	0.98 (0.89–1.09)	0.757	
	N0	-	-	
ER	Negative	1.24 (1.10–1.40)	**<.001**	**0.001**
	Unknown	1.25 (0.90–1.74)	0.181	
	Positive	-	-	
PR	Negative	1.30 (1.17–1.44)	**<.001**	**<.001**
	Unknown	1.08 (0.79–1.48)	0.621	
	Positive	-	-	
Surgical Margins	Positive	1.38 (1.27–1.50)	**<.001**	**<.001**
	Unknown	1.27 (1.09–1.48)	**0.003**	
	Negative	-	-	
Chemotherapy at any CoC Facility	No	1.30 (1.16–1.45)	**<.001**	**<.001**
	Unknown	0.94 (0.73–1.22)	0.648	
	Yes	-	-	
Hormone Therapy at any CoC Facility	No	1.29 (1.15–1.44)	**<.001**	**<.001**
	Unknown	0.74 (0.57–0.95)	**0.018**	
	Yes	-	-	
Systemic Therapy	No	1.22 (1.05–1.42)	**0.011**	**0.019**
	Unknown	1.54 (0.91–2.60)	0.110	
	Yes	-	-	
Radiation Therapy at any CoC Facility	No	1.24 (1.15–1.34)	**<.001**	**<.001**
	Unknown	0.75 (0.53–1.04)	0.087	
	Yes	-	-	

*Number of observations in the original data set = 5201. Number of observations used = 4997.

**Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Percent No High School Degree Quartiles 2000, and Diagnosis Year (quartile).

Table 5:

Association with Survival - Propensity Score Matched Sample

	Local Surgery	N	Hazard Ratio (95% CI)	HR P-value
Surgery at Primary Site (Regardless of Systemic Therapy)	Yes	2867	0.68 (0.63–0.72)	**<.001**
	No	2867	-	-
Surgery at Primary Site (Systemic Therapy)	Yes	2380	0.66 (0.62–0.71)	**<.001**
	No	2380	-	-
Surgery at Primary Site (No Systemic Therapy)	Yes	414	0.54 (0.47–0.63)	**<.001**
	No	414	-	-

•After propensity score matching, the study cohorts are balance among below variables: Race, Charlson-Deyo Score, Facility Location, Facility Type, Primary Payor, median income, grade, analytic T and N stage, ER, PR, Systemic Therapy, Radiation therapy, Tumor size (quartile), and age.