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ORIGINAL ARTICLE – BREAST ONCOLOGY

Effect of Surgery Type on Time to Adjuvant Chemotherapy and Impact of Delay on Breast Cancer Survival: A National Cancer Database Analysis

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ABSTRACT

Background. Timeliness of care is emerging as a quality indicator for breast cancer care. We sought to evaluate the impact of surgical treatment type on time to adjuvant chemotherapy and impact of treatment delay on survival.

Methods. Patients with stage I–III breast cancer treated with both surgery and adjuvant chemotherapy from 2010 to 2014 were identified from the National Cancer Database (NCDB). Delay in treatment was defined as>120 days from diagnosis to chemotherapy. Multivariable analysis was performed to assess factors associated with delay in treatment and the effect of treatment delay on overall survival.

Results. Of 172,043 patients identified, 89.5% initiated chemotherapy within 120 days of diagnosis. Median time from diagnosis to surgery was shorter in patients undergoing breast conservation (25 days) than mastectomy (29 days, $p<0.001$) and within mastectomy patients was shorter for mastectomy without reconstruction (26 versus 35 days, $p<0.001$). Time from diagnosis to surgery showed larger differences between surgical groups than time from surgery to chemotherapy. On multivariable analysis of mastectomy patients, reconstruction remained significantly associated with delay to chemotherapy [odds ratio (OR) 1.7, $p<0.001$]. For all patients regardless of type of surgery, after adjusting for patient, clinical, and treatment factors, delay of>120 days from diagnosis to chemotherapy was associated with worse overall survival [hazard ratio (HR) 1.29, $p<0.001$].

Conclusions. Initiation of chemotherapy greater than 120 days after diagnosis was associated with poorer overall survival. Time interval from diagnosis to surgery had the greatest impact on time from diagnosis to chemotherapy, with reconstruction resulting in the greatest delay.

Increasing interest from government payers, more informed patients, and the availability of shared outcome data have driven study of quality improvement and standardization of healthcare nationwide over the past several decades.[1,2] This has extended to breast cancer care, with the focus reaching beyond mortality and morbidity to timeliness of care delivery and efficiency.[3,4]

Timeliness in cancer care is a concern for both patients and physicians subjectively, and a growing body of data suggests its importance to oncologic outcomes.[5–7] Study of timeliness in breast cancer is complicated given the multidisciplinary nature of its treatment. Multimodality treatment allows for ample opportunity for variation in treatment, surgical options, and access to care issues, which all contribute to the complexity. While some previous studies were inconclusive or found no correlation between timing of breast cancer care and overall survival, these were thought to be underpowered or measures of delay were not set at a clinically relevant threshold.[8–11] Several recent studies have suggested that there are detrimental effects of long intervals between diagnosis of breast cancer and initiation of adjuvant therapy.[12–14] Of interest, this new body of data has led to the Commission on Cancer (CoC)

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incorporating receipt of systemic chemotherapy within 120 days of diagnosis as a quality metric for patients under the age of 70 years with hormone receptor-negative cancers.[15]

Studies utilizing national databases and registries were able to demonstrate a correlation between oncologic outcomes and timeliness. Subgroup analysis pointed to patient-, treatment-, and process-related factors that may contribute to delay.[15–18] The aim of this study is to evaluate the influence of type of surgical treatment on time to chemotherapy by comparing groups based on breast conservation and mastectomy, and also within the mastectomy group to evaluate the impact of immediate breast reconstruction. We focus on evaluating both the time interval from diagnosis to surgery as well as the interval from surgery to chemotherapy and compare the influence of surgical management on both intervals. We hypothesized that a larger operation (mastectomy with immediate reconstruction) which is associated with higher risk of complications may delay initiation of chemotherapy after surgery, and therefore that this delay would be dependent on surgery type.

The goal of this study is to use the National Cancer Database to evaluate how type of breast surgery impacted timing to adjuvant chemotherapy and factors that influenced any delay in therapy, and furthermore, to evaluate the impact of any delay in adjuvant chemotherapy on patient outcome.

PATIENTS AND METHODS

Patients diagnosed with pathologic stage I–III breast cancer by the American Joint Committee on Cancer (AJCC) 7th edition staging guidelines between 2010 and 2014 were identified from the NCDB participant user file.[19] The study cohort was limited to patients who underwent surgery and received adjuvant chemotherapy, defined as chemotherapy starting from 1 to 365 days after first surgery. Patients who had inflammatory breast cancer or metastatic disease were excluded, as were patients who underwent neoadjuvant chemotherapy, endocrine or radiation therapy. Patients for whom the surgical treatment could not be clearly defined based on the data in the NCDB were excluded. As recommended by NCDB guidelines, we also excluded patients who underwent no treatment at the reporting facility and those with prior history of cancer. The National Cancer Database (NCDB) collects patient demographics, tumor, treatment, and outcomes variables from more than 1500 CoC-accredited cancer facilities, capturing over 70% of all new cancer diagnoses in the country every year.[20] Data from the NCDB are retrospective and deidentified, ensuring confidentiality. This study was determined to be exempt from review by our local institutional review board.

In the NCDB, timing intervals are provided with respect to the first surgery and the most definitive surgery. Our primary analysis used the time from diagnosis to first surgery, but we also performed a sensitivity analysis looking at the time from diagnosis to most definitive surgery. The time from diagnosis to first surgery, the time from first surgery to first dose of chemotherapy, and the total time from diagnosis to first dose of chemotherapy were determined. We defined a delay in chemotherapy as any case with greater than a 120-day time interval from diagnosis to first dose of chemotherapy. This mirrored the established CoC quality metric, but we applied this across all tumor types.

The type of surgery was classified as breast conservation (BCS) or mastectomy. Additionally, mastectomy patients were subdivided into mastectomy with immediate breast reconstruction (M+IBR) and mastectomy without immediate breast reconstruction (M–IBR). Contralateral prophylactic mastectomy (CPM) was assessed in the entire mastectomy cohort. Estrogen receptor (ER) and progesterone receptor (PR) status were recorded as positive if $\geq$ 1% of cells stained positive. Hormone receptor (HR)-positive tumors included ER- and/or PR-positive results. Human epidermal growth factor receptor (HER2) status was recorded from a summary of results including immunohistochemistry, fluorescence in situ hybridization, and chromogenic in situ hybridization when performed. Approximated biologic subtype was classified as HER2+, HR+/HER2–, or triple-negative breast cancer (TNBC) for those ER–/PR–/HER2–. The potential impact of postsurgical complications on time to chemotherapy was assessed using the NCDB variable capturing hospital readmission within 30 days of surgical discharge.

Statistical Analysis

Timing variables were summarized using the median and interquartile range (IQR). Wilcoxon rank-sum tests were used to compare timing variables between groups. Factors associated with chemotherapy delay, defined as $>$ 120 days from diagnosis to chemotherapy start, were assessed using Chi square tests for univariate analysis and logistic regression for multivariable analysis. Overall survival (OS) was analyzed using multivariable Cox proportional hazards regression to estimate the adjusted effect of chemotherapy delay on survival. Since chemotherapy delay is not information that would be known at baseline (diagnosis date), we used time from chemotherapy start to death or last follow-up as the time variable in modeling the effect of chemotherapy delay on survival. Survival models adjusted for age, sex, Charlson–

Deyo comorbidity score, race, ethnicity, insurance status, pathologic tumor–node–metastasis (TNM) stage, grade, biologic subtype, surgery type, adjuvant radiation, and adjuvant endocrine therapy were calculated. Adjusted survival estimates were calculated in patients with and without chemotherapy delay using inverse probability weights to balance the two groups with respect to other covariates.[21] Analysis was performed using SAS (version 9.4). p-Values<0.05 were considered statistically significant.

RESULTS

A total of 172,043 patients with stage I–III breast cancer treated with surgery followed by adjuvant chemotherapy and meeting study criteria were identified. Patient characteristics are presented in Table 1, revealing that 90,488 patients (52.6%) underwent breast conservation. Within the 81,555 patients who underwent mastectomy, 35,302 (43.3%) had immediate reconstruction and 31,615 (38.8%) had CPM.

Time from Diagnosis to First Surgery

The median time from diagnosis to surgery for the entire cohort was 27 days (IQR 16–41 days). Patients who underwent BCS had significantly shorter time from diagnosis to surgery (median 25 days) when compared with those who underwent mastectomy (median 29 days, $p<0.001$). Those who underwent reconstruction (M+IBR) had longer median interval to surgery (35 days) compared with those who did not undergo immediate reconstruction (M–IBR) (26 days, $p<0.001$, Table 2). Patients who underwent tissue-based reconstruction had a similar interval to surgery to those who underwent implant-based reconstruction (median 35 days). Time to first surgery showed a small but statistically significant difference between those undergoing therapeutic mastectomy with CPM (median 31 days) and those who underwent therapeutic mastectomy only (median 29 days, $p<0.001$) on unadjusted analysis.

Time from First Surgery to Chemotherapy

The median time from first surgery to first dose of chemotherapy was 43 days for the entire cohort. Due to the large sample, every comparison of time variables between surgery groups was statistically significant ($p<0.001$). However, the differences with respect to time from surgery to chemotherapy were small and not clinically significant with a median of 43–44 days for each surgery group: BCS (43 days) versus mastectomy (44 days), and within the mastectomy subset M+IBR (44 days) and M–IBR (44 days, Table 2). There was a slightly longer interval from surgery to initiation of chemotherapy for patients who underwent tissue-based reconstruction (median 45 days) compared with those who underwent implant-based reconstruction (median 44 days, $p<0.001$). Those patients who underwent CPM had slightly shorter time from surgery to chemotherapy compared with those without CPM (median 43 versus 45 days, $p<0.001$).

Overall Time from Diagnosis to Chemotherapy

The median time to chemotherapy (TTC) was 74 days (IQR 57–96 days) for the entire cohort, and 89.5% of patients started chemotherapy within 120 days of diagnosis. Patients who underwent BCS had shorter overall TTC (median 71 days) compared with those who had mastectomy (median 78 days, $p<0.001$). Patients who had BCS were less likely to have a delay to chemotherapy, with 8.3% starting chemotherapy greater than 120 days after diagnosis compared with 12.9% of the overall mastectomy group ($p<0.001$). Patients who had M+IBR had longer overall TTC (median 84 days) compared with the M–IBR subgroup (median 74 days, $p<0.001$). In terms of meeting the 120-day metric, 15.0% of those with immediate reconstruction had a delay compared with 11.3% of mastectomy patients without immediate reconstruction ($p<0.001$, Table 2). Upon evaluation of type of reconstruction, 16.0% of patients who underwent tissue-based reconstruction had a delay compared with 13.3% of patients who underwent implant-based reconstruction ($p<0.001$).

Multivariable Analysis of Factors Associated with Chemotherapy Delay

In addition to type of breast surgery, several other factors were associated with delay in TTC (i.e.,>120 days from diagnosis to chemotherapy start). With respect to biologic subtype, patients with TNBC were least likely to experience a delay (7.4%), followed by HER2+(10.3%) then HR+/HER2– (11.6%), and similar trends were observed for other timing variables (Supplementary Table 1). Multivariable analysis for the outcome of chemotherapy delay was performed separately for BCS and mastectomy patients (Tables 3, 4). Patient factors associated with chemotherapy delay included increasing age, higher comorbidity score, Black race, and primary payor other than private insurance. Patients with stage II or III disease and triple-negative or HER2+biologic subtype were less likely to have a delay in chemotherapy start. After adjusting for these factors in the mastectomy subgroup, reconstruction remained significantly associated with chemotherapy delay [OR 1.71, 95% confidence interval (CI) 1.64–1.80].

TABLE 1 Patient demographics and clinical characteristics

	BCS (*N*=90,488)	Mastectomy w/o reconstruction (*N*=46,253)	Mastectomy with reconstruction (*N*=35,302)	Total (*N*=172,043)	*p* Value
Age at diagnosis (years)					<0.0001[1*]
N	90,488	46,253	35,302	172,043	
Mean (SD)	56.9 (10.5)	57.1 (12.0)	49.5 (10.2)	55.4 (11.3)	
Median	57.0	57.0	49.0	55.0	
Q1, Q3	49.0, 64.0	48.0, 66.0	42.0, 57.0	47.0, 64.0	
Range	(20.0–90.0)	(20.0–90.0)	(18.0–90.0)	(18.0–90.0)	
Age group (years)					<0.0001[2*]
<40	4271 (4.7%)	3497 (7.6%)	5645 (16.0%)	13,413 (7.8%)	
40–49	18,488 (20.4%)	9276 (20.1%)	12,787 (36.2%)	40,551 (23.6%)	
50–59	30,111 (33.3%)	13,212 (28.6%)	10,642 (30.1%)	53,965 (31.4%)	
60–69	27,202 (30.1%)	12,920 (27.9%)	5344 (15.1%)	45,466 (26.4%)	
70–79	9342 (10.3%)	6301 (13.6%)	857 (2.4%)	16,500 (9.6%)	
80+	1074 (1.2%)	1047 (2.3%)	27 (0.1%)	2148 (1.2%)	
Sex					<0.0001[2*]
Male	365 (0.4%)	1190 (2.6%)	96 (0.3%)	1651 (1.0%)	
Female	90,123 (99.6%)	45,063 (97.4%)	35,206 (99.7%)	170,392 (99.0%)	
Charlson–Deyo score					<0.0001[2*]
0	76,948 (85.0%)	37,641 (81.4%)	31,385 (88.9%)	145,974 (84.8%)	
1	11,430 (12.6%)	7069 (15.3%)	3468 (9.8%)	21,967 (12.8%)	
2	1721 (1.9%)	1237 (2.7%)	384 (1.1%)	3342 (1.9%)	
≥3	389 (0.4%)	306 (0.7%)	65 (0.2%)	760 (0.4%)	
Race					<0.0001[2*]
Missing	797	319	284	1400	
White	72,084 (80.4%)	37,244 (81.1%)	29,688 (84.8%)	139,016 (81.5%)	
Black	13,643 (15.2%)	6055 (13.2%)	3671 (10.5%)	23,369 (13.7%)	
Other	3964 (4.4%)	2635 (5.7%)	1659 (4.7%)	8258 (4.8%)	
Spanish/Hispanic origin					<0.0001[2^]
Missing	3219	1643	1032	5894	
No Spanish/Hispanic origin	81,935 (93.9%)	41,574 (93.2%)	32,221 (94.0%)	155,730 (93.7%)	
Spanish/Hispanic origin	5334 (6.1%)	3036 (6.8%)	2049 (6.0%)	10,419 (6.3%)	
Primary payor					<0.0001[2*]
Missing	1396	524	269	2189	
Not insured	2089 (2.3%)	1626 (3.6%)	487 (1.4%)	4202 (2.5%)	
Private insurance	57,175 (64.2%)	25,130 (55.0%)	28,601 (81.6%)	110,906 (65.3%)	
Medicaid	7002 (7.9%)	4861 (10.6%)	2328 (6.6%)	14,191 (8.4%)	
Medicare	21,723 (24.4%)	13,460 (29.4%)	3169 (9.0%)	38,352 (22.6%)	
Other government	1103 (1.2%)	652 (1.4%)	448 (1.3%)	2203 (1.3%)	
Biologic subtype					<0.0001[2*]
Missing	2460	1317	794	4571	
HER2+	16,454 (18.7%)	9344 (20.8%)	6573 (19.0%)	32,371 (19.3%)	
Triple negative	21,734 (24.7%)	8856 (19.7%)	5845 (16.9%)	36,435 (21.8%)	
HR+/HER2–	49,840 (56.6%)	26,736 (59.5%)	22,090 (64.0%)	98,666 (58.9%)	
Pathologic stage group					<0.0001[2*]
Missing	3409	1862	1104	6375	
Stage 1	39,096 (44.9%)	8233 (18.5%)	9990 (29.2%)	57,319 (34.6%)	
Stage 2	40,625 (46.7%)	22,315 (50.3%)	17,544 (51.3%)	80,484 (48.6%)	
Stage 3	7358 (8.4%)	13,843 (31.2%)	6664 (19.5%)	27,865 (16.8%)	

TABLE 1 continued

	BCS (*N*=90,488)	Mastectomy w/o reconstruction (*N*=46,253)	Mastectomy with reconstruction (*N*=35,302)	Total (*N*=172,043)	*p* Value
Grade					<0.0001[2*]
Missing	4369	2321	1727	8417	
Well differentiated	7994 (9.3%)	3646 (8.3%)	3086 (9.2%)	14,726 (9.0%)	
Moderately differentiated	31,939 (37.1%)	17,459 (39.7%)	14,190 (42.3%)	63,588 (38.9%)	
Poorly differentiated/undifferentiated	46,186 (53.6%)	22,827 (52.0%)	16,299 (48.5%)	85,312 (52.1%)	
Radiation therapy					<0.0001[2*]
Missing	123	195	178	496	
No radiation	5411 (6.0%)	24,705 (53.6%)	22,180 (63.1%)	52,296 (30.5%)	
Radiation	84,954 (94.0%)	21,353 (46.4%)	12,944 (36.9%)	119,251 (69.5%)	
Hormone therapy					<0.0001[2*]
Missing	2142	979	732	3853	
No hormone therapy	31,935 (36.1%)	15,368 (33.9%)	9961 (28.8%)	57,264 (34.0%)	
Hormone therapy	56,411 (63.9%)	29,906 (66.1%)	24,609 (71.2%)	110,926 (66.0%)	
[+]Readmission					<0.0001[2+]
Missing	1814	857	472	3143	
No readmission	84,107 (94.8%)	42,864 (94.4%)	32,650 (93.7%)	159,621 (94.5%)	
Yes readmission	4567 (5.2%)	2532 (5.6%)	2180 (6.3%)	9279 (5.5%)	

[1]Kruskal–Wallis

[2]Chi square

[*]Each pairwise $p<0.001$

[^]Pairwise comparison BCS versus mastectomy with reconstruction ($p=0.38$), BCS versus mastectomy with reconstruction ($p<0.001$), and mastectomy with reconstruction versus mastectomy with no reconstruction ($p<0.001$)

[+]Pairwise comparison BCS versus mastectomy with no reconstruction ($p=0.001$), BCS versus mastectomy with reconstruction ($p<0.001$), and mastectomy with reconstruction versus mastectomy with no reconstruction ($p<0.001$)

Multivariable Analysis of Factors Associated with Overall Survival

Median follow-up time from diagnosis was 46 months. Analyzing all surgery types together, a multivariable Cox proportional hazards regression model adjusted for patient, clinical, and treatment factors showed that chemotherapy delay (i.e.,>120 days from diagnosis to chemotherapy versus≤120 days) was associated with worse overall survival (HR 1.29, 95% CI 1.22–1.37, $p<0.001$). We also examined models stratified by biologic subtype and confirmed a significant effect within each subtype. The hazard ratios for chemotherapy delay were 1.47 (95% CI 1.29–1.68), 1.23 (95% CI 1.10–1.38), and 1.23 (95% CI 1.13–1.34) for HER2+, TNBC, and HR+/HER2–, respectively (Fig. 1). Adjusted estimates of 5-year OS showed absolute differences between those with chemotherapy delay versus without of 88.6% versus 91.1% (overall), 90.9% versus 92.6% (HR+/HER2–), 89.1% versus 92.7% (HER2+), and 83.4% versus 85.5% (TNBC).

Further, we assessed the impact of shorter timeframes from diagnosis to chemotherapy; the only threshold that was associated with a statistically significant increase in risk was>120 day time from diagnosis to chemotherapy. Specifically, the hazard ratios were 0.96 (95% CI 0.91–1.00) for 61–90 days, 1.01 (95% CI 0.96–1.07) for 91–120 days, and 1.27 (95% CI 1.19–1.35) for>120 days, each compared with chemotherapy starting within 60 days of diagnosis in the overall model. Results were similar when examined separately for each biologic subtype.

DISCUSSION

In a large cohort of patients treated with upfront surgery followed by adjuvant chemotherapy, we found that time interval of greater than 120 days from diagnosis to initiation of chemotherapy was associated with poorer overall survival. Contrary to what was hypothesized, more extensive surgery did not lead to a clinically significant delay between surgery and initiation of chemotherapy; however, mastectomy with reconstruction was associated with longer TTC due to a longer time interval from diagnosis to date of surgery.

In two previous large single-institution studies, no difference was seen in time from surgery to initiation of

TABLE 2 Effect of type of surgery on time to treatment

	BCS (*N*=90,488)	Mastectomy (*N*=81,555)	*p*-Value	No reconstruction (*N*=46,253)	Yes reconstruction (*N*=35,302)	*p*-Value
First surgical procedure, days from Dx			<0.0001[1]			<0.0001[1]
N	90,488	81,555		46,253	35,302	
Mean (SD)	28.3 (22.5)	33.1 (26.0)		29.7 (25.7)	37.5 (25.7)	
Median	25.0	29.0		26.0	35.0	
Q1, Q3	15.0, 37.0	17.0, 44.0		15.0, 40.0	22.0, 49.0	
Range	(0.0–879.0)	(0.0–1113.0)		(0.0–1113.0)	(0.0–810.0)	
Diagnosis to chemo start (days)			<0.0001[1]			<0.0001[1]
N	90,488	81,555		46,253	35,302	
Mean (SD)	77.0 (35.0)	84.8 (38.1)		81.2 (38.4)	89.5 (37.3)	
Median	71.0	78.0		74.0	84.0	
Q1, Q3	55.0, 91.0	61.0, 101.0		57.0, 97.0	65.0, 106.0	
Range	(1.0–914.0)	(1.0–1153.0)		(1.0–1153.0)	(1.0–864.0)	
First surgery to chemo start (days)			<0.0001[1]			0.0002[1]
N	90,488	81,555		46,253	35,302	
Mean (SD)	48.7 (27.1)	51.7 (29.1)		51.5 (29.2)	51.9 (28.9)	
Median	43.0	44.0		44.0	44.0	
Q1, Q3	33.0, 58.0	34.0, 62.0		34.0, 62.0	34.0, 62.0	
Range	(1.0–365.0)	(1.0–349.0)		(1.0–348.0)	(1.0–349.0)	
Definitive surgery to chemo start (days)			<0.0001[1]			<0.0001[1]
N	88,851	77,643		44,363	33,280	
Mean (SD)	44.6 (25.2)	45.9 (23.6)		45.8 (24.4)	46.0 (22.5)	
Median	40.0	41.0		41.0	42.0	
Q1, Q3	30.0, 53.0	32.0, 54.0		31.0, 54.0	33.0, 54.0	
Range	(0.0–360.0)	(0.0–333.0)		(0.0–329.0)	(0.0–333.0)	
Diagnosis to chemo≤120 days			<0.0001[2]			<0.0001[2]
No	7551 (8.3%)	10,515 (12.9%)		5234 (11.3%)	5281 (15.0%)	
Yes	82,937 (91.7%)	71,040 (87.1%)		41,019 (88.7%)	30,021 (85.0%)	

[1]Kruskal–Wallis

[2]Chi square

chemotherapy between patients who underwent breast conservation and surgery.[17], [18] However, Chavez et al. found that reconstruction did contribute to an increase in this time interval. The NCDB includes data on 30-day readmission, which we looked at as a possible surrogate for postoperative complications. When this was considered in the multivariable analysis, it was not found to contribute to delay. The significance of this is not clear given that readmission is an oversimplified surrogate for complications, since many complications do not involve readmission or may occur after 30 days. When we looked at the M+IBR subgroup according to type of reconstruction, there was a slightly greater delay between surgery and chemotherapy start for patients who underwent tissue-based reconstruction compared with implant-based reconstruction, and patients undergoing tissue-based reconstruction were slightly more likely to have a delay in chemotherapy (16% versus 13% with>120 days from diagnosis to chemotherapy start).

Time from diagnosis to surgery was found to be the most variable time interval when evaluating TTC according to type of surgery. While a direct relationship between treatment delay and survival cannot be made in this study, we did observe that time from diagnosis to chemotherapy greater than 120 days was associated with poorer overall survival on multivariable analysis adjusted for factors including age, comorbidities, disease stage, biologic subtype, and other treatments received. Patients who underwent more extensive surgery, i.e., mastectomy with reconstruction, did have a greater time interval to surgery from initial diagnosis. On multivariable analysis, reconstruction remained a significant predictor of delay. While the differences in time to surgery were statistically significant, the clinical significance of a 4-day difference in

TABLE 3 Logistic regression model predicting>120 days from diagnosis to adjuvant chemotherapy start among mastectomy patients

Variable	Level	Univariate odds ratio (95% CI)	*p*-Value	Multivariable odds ratio (95% CI)	*p*-Value
Age group (years)	<40	1.0 reference		1.0 reference	
	40–49	1.37 (1.26, 1.48)	<0.001	1.47 (1.35, 1.59)	<0.001
	50–59	1.44 (1.33, 1.55)	<0.001	1.66 (1.53, 1.80)	<0.001
	60–69	1.48 (1.37, 1.60)	<0.001	1.76 (1.61, 1.93)	<0.001
	70–79	1.28 (1.16, 1.41)	<0.001	1.61 (1.43, 1.81)	<0.001
	80+	1.24 (1.02, 1.51)	0.030	1.83 (1.48, 2.26)	<0.001
Sex	Female	1.0 reference		1.0 reference	
	Male	0.63 (0.52, 0.76)	<0.001	0.64 (0.53, 0.78)	<0.001
Charlson–Deyo score	0	1.0 reference		1.0 reference	
	1	1.28 (1.21, 1.36)	<0.001	1.20 (1.13, 1.28)	<0.001
	2	1.46 (1.28, 1.66	<0.001	1.36 (1.19, 1.56)	<0.001
	≥ 3	2.80 (2.23, 3.52)	<0.001	2.51 (1.99, 3.18)	<0.001
Race	White	1.0 reference		1.0 reference	
	Black	2.12 (2.01, 2.23)	<0.001	2.22 (2.10, 2.35)	<0.001
	Other	1.33 (1.22, 1.45)	<0.001	1.32 (1.21, 1.45)	<0.001
	Unknown	1.23 (0.97, 1.55)	0.084	1.12 (0.88, 1.43)	0.372
Spanish/Hispanic origin	No Spanish/Hispanic origin	1.0 reference		1.0 reference	
	Spanish/Hispanic origin	2.04 (1.90, 2.18)	<0.001	2.08 (1.93, 2.24)	<0.001
	Unknown	0.91 (0.80, 1.02)	0.115	0.96 (0.85, 1.09)	0.529
Primary payor	Private insurance	1.0 reference		1.0 reference	
	Medicaid	2.43 (2.29, 2.58)	<0.001	2.34 (2.19, 2.50)	<0.001
	Medicare	1.29 (1.22, 1.35)	<0.001	1.38 (1.29, 1.48)	<0.001
	Not insured	1.96 (1.75, 2.19)	<0.001	1.93 (1.72, 2.17)	<0.001
	Other government	1.49 (1.26, 1.76)	< 0.001	1.53 (1.29, 1.81)	< 0.001
	Insurance status unknown	1.60 (1.32, 1.93)	< 0.001	1.66 (1.36, 2.01)	< 0.001
Reconstruction	No reconstruction	1.0 reference		1.0 reference	
	Yes reconstruction	1.38 (1.32, 1.44)	< 0.001	1.71 (1.64, 1.80)	< 0.001
CPM	No CPM	1.0 reference		1.0 reference	
	Yes CPM	0.82 (0.78,0.85)	< 0.001	0.88 (0.84, 0.92)	< 0.001
Biologic subtype	HR+/HER2–	1.0 reference		1.0 reference	
	HER2+	0.86 (0.82, 0.91)	< 0.001	0.80 (0.76, 0.85)	< 0.001
	Triple negative	0.65 (0.61, 0.69)	< 0.001	0.57 (0.53, 0.60)	< 0.001
	Unknown	1.02 (0.90, 1.16)	0.710	0.99 (0.87, 1.13)	0.884
Pathologic stage group	Stage 1	1.0 reference		1.0 reference	
	Stage 2	0.84 (0.80, 0.88)	< 0.001	0.77 (0.73, 0.81)	< 0.001
	Stage 3	0.75 (0.71, 0.80)	< 0.001	0.65 (0.61, 0.70)	< 0.001
	Unknown	0.80 (0.71, 0.90)	< 0.001	0.77 (0.68, 0.87)	< 0.001
Readmission	No readmission	1.0 reference		1.0 reference	
	Yes readmission	1.04 (0.96, 1.14)	0.324	1.01 (0.92, 1.10)	0.825
	Unknown	1.18 (1.01, 1.38)	0.032	1.24 (1.06, 1.46)	0.006

median time between BCS and mastectomy may be questionable. The 9-day difference in median time between M+ IBR and M–IBR is more clinically significant. Bleicher et al. also showed that>61 days interval in time to surgery was associated with worse OS; however, their cohort consisted mostly of patients who did not undergo chemotherapy and had smaller tumors with fewer at advanced stage.[15] Time to surgery has been previously shown to be increasing, and the current study identifies some potential targets for intervention to reduce wait times. Potential causes of delay specifically associated with M+ IBR include additional consultations, availability of plastic

TABLE 4 Logistic regression model predicting>120 days from diagnosis to adjuvant chemotherapy start among BCS patients

Variable	Level	Univariate odds ratio (95% CI)	*p*-Value	Multivariable odds ratio (95% CI)	*p*-Value
Age group (years)	< 40	1.0 reference		1.0 reference	
	40–49	1.05 (0.93, 1.19)	0.417	1.17 (1.03, 1.32)	0.017
	50–59	1.05 (0.93, 1.18)	0.451	1.26 (1.12, 1.43)	< 0.001
	60–69	1.08 (0.96, 1.22)	0.198	1.30 (1.15, 1.48)	< 0.001
	70–79	1.17 (1.02, 1.34)	0.020	1.38 (1.19, 1.60)	< 0.001
	80+	1.73 (1.40, 2.14)	< 0.001	2.12 (1.69, 2.65)	< 0.001
Sex	Female	1.0 reference		1.0 reference	
	Male	0.98 (0.68, 1.43)	0.931	0.98 (0.67, 1.43)	0.907
Charlson–Deyo score	0	1.0 reference		1.0 reference	
	1	1.18 (1.10, 1.27)	< 0.001	1.04 (0.97, 1.12)	0.274
	2	1.27 (1.09, 1.49)	0.003	1.10 (0.93, 1.29)	0.258
	≥ 3	1.63 (1.21, 2.20)	0.001	1.36 (1.00, 1.85)	0.047
Race	White	1.0 reference		1.0 reference	
	Black	2.00 (1.89, 2.12)	< 0.001	2.21 (2.08, 2.35)	< 0.001
	Other	1.63 (1.47, 1.80)	< 0.001	1.60 (1.44, 1.78)	< 0.001
	Unknown	1.54 (1.23, 1.93)	< 0.001	1.40 (1.10, 1.77)	0.006
Spanish/Hispanic origin	No Spanish/Hispanic origin	1.0 reference		1.0 reference	
	Spanish/Hispanic origin	2.37 (2.20, 2.56)	< 0.001	2.28 (2.10, 2.47)	< 0.001
	Unknown	1.01 (0.88, 1.15)	0.930	1.0 (0.87, 1.14)	0.984
Primary payor	Private insurance	1.0 reference		1.0 reference	
	Medicaid	2.69 (2.50, 2.89)	< 0.001	2.23 (2.07, 2.41)	< 0.001
	Medicare	1.48 (1.40, 1.56)	< 0.001	1.41 (1.31, 1.51)	< 0.001
	Not insured	3.32 (2.96, 3.73)	< 0.001	2.74 (2.44, 3.09)	< 0.001
	Other government	1.71 (1.41, 2.07)	< 0.001	1.62 (1.34, 1.98)	< 0.001
	Insurance status unknown	1.56 (1.31, 1.87)	< 0.001	1.44 (1.20, 1.73)	< 0.001
Biologic subtype	HR+/HER2–	1.0 reference		1.0 reference	
	HER2+	0.89 (0.84, 0.95)	< 0.001	0.84 (0.79, 0.89)	< 0.001
	Triple negative	0.62 (0.58, 0.66)	< 0.001	0.53 (0.49, 0.56)	< 0.001
	Unknown	0.99 (0.86, 1.14)	0.886	0.92 (0.80, 1.06)	0.251
Pathologic stage group	Stage 1	1.0 reference		1.0 reference	
	Stage 2	0.97 (0.92, 1.02)	0.258	0.86 (0.81, 0.90)	< 0.001
	Stage 3	1.09 (1.00, 1.19)	0.043	0.88 (0.81, 0.97)	0.007
	Unknown	1.17 (1.04, 1.32)	0.008	1.08 (0.95, 1.22)	0.242
Readmission	No readmission	1.0 reference		1.0 reference	
	Yes readmission	0.99 (0.89, 1.10)	0.810	0.95 (0.85, 1.06)	0.328
	Unknown	1.25 (1.07, 1.46)	0.004	1.20 (1.03, 1.41)	0.022

surgeons, and availability of longer operating room time slots.

Although the CoC quality metric is limited to patients under age 70 years with hormone receptor-negative disease, we found that a time interval from diagnosis to chemotherapy of>120 days was associated with poorer survival within each biologic subtype. Although the effect was significant within every subtype, the largest effect size was for HER2+patients in our study. Other studies focusing on time from surgery to adjuvant chemotherapy have found increased sensitivity to delay and worsening survival in patients with HER2+disease and TNBC relative to hormone receptor-positive disease.[17,18]

While the NCDB offers the opportunity to study a large number of patients, there are many limitations. Most importantly there is a lack of information regarding specific chemotherapy regimen and length of treatment, and no information regarding whether the planned chemotherapy was completed. Also, recurrence and breast cancer-specific survival outcomes are not available through the NCDB, so

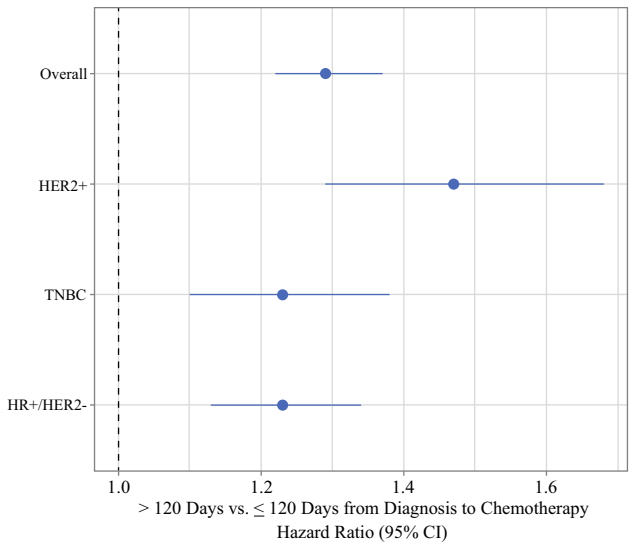

FIG. 1 Forest plot of multivariable adjusted hazard ratios for the effect of an interval>120 days versus≤120 days from diagnosis to chemotherapy on overall survival (OS), overall and for each biologic subtype

the outcome analysis is limited to overall survival. There are many variables that contribute to OS; however, our multivariable analysis adjusted for key confounding variables (e.g. age, comorbidities, and stage) continued to show a significant effect for chemotherapy delay. Similarly, there are many factors that contribute to timeliness of care, many of which may not be captured by the data available from the NCDB.

CONCLUSIONS

While the majority of work on time to chemotherapy has focused on the interval from surgery to chemotherapy, we demonstrated that time from diagnosis to surgery was in fact the time period with the greatest variability and therefore had the greatest influence on the overall time interval from diagnosis to adjuvant chemotherapy. Patients undergoing mastectomy with reconstruction had the longest TTC, and this was due mostly to longer time from diagnosis to surgery. This identifies an area for potential intervention and a need for increased access to plastic surgeons and operating room availability for these combined cases.

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