VOLUME 32 · NUMBER 8 · MARCH 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Impact of Delaying Initiation of Adjuvant Chemotherapy in Patients With Breast Cancer

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Processed as a Rapid Communication manuscript. See accompanying editorial on page 717.
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Published online ahead of print at www.jco.org on January 27, 2014.

Supported in part by Grant No. 1K23CA121994-01 from the National Cancer Institute of the National Institutes of Health (A.M.G.-A.), Komen for the Cure Catalyst Award No. KG090341 (A.M.G.-A.), Research Scholar Grant No. 121329-RSG-11-187-01-TBG from the American Cancer Society (A.M.G.-A.), and Cancer Center Support Grant No. 2P30 CA016672 (PP-RP6) from the Department of Health and Human Services, National Institutes of Health, National Cancer Institute (to the MD Anderson Cancer Center). The MD Anderson Breast Cancer Management System and the Breast Tumor Bank are supported in part by the Nelly B. Connally Breast Cancer Research Fund.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/14/3208w-735w/$20.00

DOI: 10.1200/JCO.2013.49.7693

ABSTRACT

Purpose
For patients with breast cancer (BC), the optimal time to initiation of adjuvant chemotherapy (TTC) after definitive surgery is unknown. We evaluated the association between TTC and survival according to breast cancer subtype and stage at diagnosis.

Patients and Methods
Women diagnosed with BC stages I to III between 1997 and 2011 who received adjuvant chemotherapy at our institution were included. Patients were categorized into three groups according to TTC: ≤ 30, 31 to 60, and ≥ 61 days. Survival outcomes were estimated and compared according to TTC and by BC subtype.

Results
Among the 6,827 patients included, the 5-year overall survival (OS), relapse-free survival (RFS), and distant RFS (DRFS) estimates were similar for the different TTC categories. Initiation of chemotherapy ≥ 61 days after surgery was associated with adverse outcomes among patients with stage II (DRFS: hazard ratio [HR], 1.20; 95% CI, 1.02 to 1.43) and stage III (OS: HR, 1.76; 95% CI, 1.26 to 2.46; RFS: HR, 1.34; 95% CI, 1.01 to 1.76; and DRFS: HR, 1.36; 95% CI, 1.02 to 1.80) BC. Patients with triple-negative BC (TNBC) tumors and those with human epidermal growth factor receptor 2 (HER2) –positive tumors treated with trastuzumab who started chemotherapy ≥ 61 days after surgery had worse survival (HR, 1.54; 95% CI, 1.09 to 2.18 and HR, 3.09; 95% CI, 1.49 to 6.39, respectively) compared with those who initiated treatment in the first 30 days after surgery.

Conclusion
TTC influenced survival outcomes in the overall study cohort. This finding was particularly meaningful for patients with stage III BC, TNBC, and trastuzumab-treated HER2-positive tumors who experienced worse outcomes when chemotherapy was delayed. Our findings suggest that early initiation of chemotherapy should be granted for patients in these high-risk groups.

J Clin Oncol 32:735-744. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Randomized clinical trials have shown a survival benefit associated with the use of adjuvant chemotherapy in early-stage breast cancer (BC).[1] It is well-known that BC is a heterogeneous disease and that certain subtypes, such as triple-negative BC (TNBC) and human epidermal growth factor receptor 2 (HER2) –positive BCs, are associated with an increased risk of recurrence, which probably influences the benefit from adjuvant chemotherapy.[2-4]

Many of the trials that have evaluated the survival benefit of adjuvant chemotherapy arbitrarily defined a particular time from surgery to the start of chemotherapy, beyond which patients were no longer eligible to participate. For most patients, adjuvant chemotherapy starts within a few weeks from surgery, but it is unclear whether a delay in initiation of therapy is associated with adverse outcomes. In addition, there is little information about the impact that the time to initiation of adjuvant chemotherapy (TTC) has according to BC subtype.

There are reasons to believe that starting chemotherapy shortly after surgery might improve survival. In animal models, after the removal of the primary tumor, a phase of accelerated growth of micrometastases associated with an increase in angiogenesis has been described.[5-7]

Mathematical models have suggested that a delay in the initiation of systemic chemotherapy could increase the probability of emerging drug-resistant micrometastatic disease.[8] Results from retrospective studies that address the relationship between the TTC and survival outcomes have been controversial. Although some studies showed a positive relationship between shorter TTC and survival,[9,10] the majority did not show any detrimental effect in postponing chemotherapy within specified time frames.[11-14] A recent meta-analysis reported that per each 4-week delay in adjuvant chemotherapy initiation, there was a 6% increase in the risk of death.[15]

Furthermore, it remains unclear whether TTC has a differential impact among the distinct BC subtypes. In this large, retrospective study, we evaluate the association between TTC and outcomes according to tumor characteristics and BC subtypes.

PATIENTS AND METHODS

Patient Population

We performed a retrospective review of the Breast Medical Oncology Institutional database at The University of Texas MD Anderson Cancer Center. We identified women with stage I to III invasive primary BC diagnosed between 1997 and 2011 who received adjuvant chemotherapy at our institution. Patients with stage IV disease are generally treated with chemotherapy with palliative intention and were consequently excluded from this study.

Data on relevant prognostic factors were extracted. We obtained information on age at diagnosis, race/ethnicity, type of surgery, tumor pathologic staging (according to the American Joint Committee on Cancer [AJCC]/International Union Against Cancer [UICC] TNM staging classification), lymphovascular invasion (LVI), tumor grade, histology, and comorbidities. We also obtained data on estrogen receptor (ER), progesterone receptor (PgR), and HER2 status. BC subtype was defined as hormone receptor–positive (ER-positive and/or PgR-positive and HER2-negative), HER2-positive (HER2-positive regardless of hormone receptor status), and TNBC (HER2-negative and hormone receptor–negative). We identified the chemotherapy received and classified it as anthracycline-based, anthracycline and taxane-based, or other type. In addition, for the HER2-positive tumors, we further categorized them as trastuzumab-treated and not trastuzumab-treated, because the use of adjuvant trastuzumab was approved in 2005. The institutional review board of The University of Texas MD Anderson Cancer Center approved this study.

Statistical Analysis

Patients were categorized according to the time (in days) from definitive surgery to adjuvant chemotherapy into one of three groups: ≤ 30 days, 31 to 60 days, and ≥ 61 days. Demographic statistics were assessed, and patient characteristics were compared according to TTC category by using χ^2 test for categorical variables and F test for continuous variables. Overall survival (OS) was measured from the date of adjuvant chemotherapy initiation to the date of death. Relapse-free survival (RFS) was measured from the date of adjuvant chemotherapy initiation to the date of first documented local or distant recurrence or last follow-up, and distant relapse-free survival (DRFS) was measured from the date of adjuvant chemotherapy initiation to the date of first documented distant recurrence or last follow-up. Patients who died before experiencing a disease recurrence were considered censored at the time of death. The Kaplan-Meier product limit method was used to estimate the 5-year OS, 5-year RFS, and 5-year DRFS with 95% CIs of all patients according to time to initiation of chemotherapy and other patient and clinical characteristics. Groups were compared by using the log-rank statistic. Subset analyses were carried out according to stage at diagnosis and BC subtype. Because these were exploratory analyses, no formal adjustments for multiple comparisons were made.

Cox proportional hazards regression models were fit to determine the association between TTC and survival outcomes after adjustment for potential confounders. Variables in the model included age (as a continuous variable), race/ethnicity, pathologic tumor size according to TNM classification (T1, T2, T3-4), pathologic nodal status according to TNM classification (N1, N2, N3), histologic grade, LVI, type of surgery, and number of comorbidities (0, 1 to 2, 3 to 4, or 5+). Within the subset of patients with HER2-positive BC, the use of trastuzumab was included as an additional covariate. Similarly, among patients with TNBC, the type of adjuvant chemotherapy (anthracycline-based *v* anthracycline and taxane-based) was included as an additional covariate. Results are expressed in hazard ratios (HRs) and 95% CIs. *P* values $\leq .05$ were considered statistically significant. All tests were two-sided. Statistical analyses were carried out by using SAS 9.2 (SAS Institute, Cary, NC) and S-Plus 7.0 (Insightful Corporation, Seattle, WA).

RESULTS

Patient Demographics and Tumor Characteristics

A total of 6,827 women were identified, and median follow-up was 59.3 months. The majority of the patients (84.5%) had stage I to II BC; only 15.5% of the patients had stage III. Patient, tumor, and treatment characteristics stratified by time to chemotherapy groups are listed in Table 1. Among the included patients, 2,716 (39.8%) received chemotherapy ≤ 30 days from surgery, 2,994 (43.8%) received chemotherapy 31 to 60 days after surgery, and 1,117 (16.4%) received chemotherapy ≥ 61 days after surgery.

There were no differences in TTC between patients who underwent breast-conserving surgery and those who underwent a mastectomy ($P = .83$). There was no association between the number of comorbidities and the TTC ($P = .6$).

At a median follow-up of 59.3 months, 1,437 patients (21.0%) had died, 2,135 (31.3%) had experienced a recurrence, and 1,924 (28.2%) had experienced a distant recurrence. Table 2 summarizes the 5-year OS, 5-year RFS, and 5-year DRFS for the overall population according to TTC and patient and tumor characteristics.

For the overall cohort, 5-year OS, 5-year RFS, and 5-year DRFS were 84%, 69%, and 72%, respectively. The 5-year OS estimate was 85%, 83%, and 83% among patients who received chemotherapy ≤ 30, 31 to 60, and ≥ 61 days after surgery, respectively ($P = .54$). Similarly, no significant differences across TTC groups were observed for RFS ($P = .67$) or DRFS ($P = .49$).

As expected, patients with larger tumors and greater lymph node involvement had lower OS, RFS, and DRFS. Worse survival estimates were seen for patients with grade 3 tumors and those with LVI. We observed that the impact on TTC initiation was different among the distinct BC subtypes. Survival estimates by TTC according to tumor subtype are shown in Table 2. No differences in OS, RFS, or DSFR were seen among patients with hormone receptor–positive or HER2-positive tumors. However, among trastuzumab-treated patients with HER2-positive tumors, the 5-year OS estimate was 88%, 87%, and 75% for patients who initiated chemotherapy ≤ 30, 31 to 60, and ≥ 61 days, respectively, after surgery ($P = .01$). Similarly, among patients with TNBC, the 5-year OS estimate was 70% for patients who started chemotherapy ≤ 30 days, 59% for those who started chemotherapy from 31 to 60 days, and 67% for those who started chemotherapy ≥ 61 days from surgery ($P = .005$). Despite the differences in OS, no differences in RFS or DRFS were seen for either the TNBC or the trastuzumab-treated patients.

The multivariable models are depicted in Table 3. After adjusting for confounders, we observed that patients who received chemotherapy ≥ 61 days from surgery had a 19% increase in the risk of death

Table 1. Patient and Clinical Characteristics by TTC Among Patients With Stage I to III BC Diagnosed Between 1997 and 2011 and Treated With Adjuvant Chemotherapy

Characteristic	All Patients (N = 6,827)		TTC (days)						
			≤ 30 (n = 2,716)		31-60 (n = 2,994)		≥ 61 (n = 1,117)		
	No.	%	No.	%	No.	%	No.	%	*P**
Age at diagnosis, years									
Median	50		49		50		50		
Range	19-85		21-83		19-85		23-82		
Race/ethnicity									.28
White	4,927	72.2	1,938	71.4	2,161	72.2	828	74.1	
African American	646	9.5	254	9.4	303	10.1	89	8.0	
Hispanic	912	13.4	376	13.8	388	13.0	148	13.2	
Other	342	5	148	5.4	142	4.7	52	4.7	
Pathologic tumor size									.56
T1	3,595	53.8	1,415	53.2	1,598	54.6	582	53.0	
T2	2,642	39.5	1,062	39.9	1,131	38.6	449	40.9	
T3	420	6.3	173	6.5	183	6.3	64	5.8	
T4	28	0.4	9	0.3	15	0.5	4	0.4	
Nodal status									.75
N0	2,804	41.7	1,101	41.1	1,258	42.7	445	40.5	
N1	2,539	37.8	1,009	37.7	1,102	37.4	428	39.0	
N2	872	13	355	13.3	371	12.6	146	13.3	
N3	506	7.5	213	8.0	214	7.3	79	7.2	
Subtype									.008
Hormone receptor–positive	3,834	65.4	1,604	67.7	1,646	64.5	584	61.9	
HER2-positive	1,142	19.5	445	18.8	493	19.3	204	21.6	
Triple-negative	889	15.2	321	13.5	412	16.2	156	16.5	
Nuclear grade									.18
I	279	4.3	101	3.9	133	4.6	45	4.3	
II	2,552	39.2	1,052	40.8	1,083	37.8	417	39.5	
III	3,671	56.5	1,424	55.3	1,652	57.6	595	56.3	
Lymphovascular invasion									.09
Negative	4,600	67.4	1,795	66.1	2,027	67.7	778	69.7	
Positive	2,227	32.6	921	33.9	967	32.3	339	30.3	
Surgery									.83
BCS	3,042	44.6	1,214	44.7	1,323	44.2	505	45.2	
Mastectomy	3,784	55.4	1,502	55.3	1,670	55.8	612	54.8	
No. of comorbidities†									.46
0	2,142	31.4	853	31.4	924	30.9	365	32.7	
1-2	2,970	43.5	1,162	42.8	1,311	43.8	497	44.5	
3-4	1,387	20.3	558	20.5	619	20.7	210	18.8	
5-12	328	4.8	143	5.3	140	4.7	45	4.0	
Trastuzumab among HER2-positive patients (n = 1,142)									.95
No	551	48.2	212	47.6	240	48.7	99	48.5	
Yes	591	51.8	233	52.4	253	51.3	105	51.5	
Adjuvant chemotherapy among triple-negative patients (n = 889)									.98
Anthracycline-based	237	26.7	84	26.2	109	26.5	44	28.2	
Anthracycline-based + taxane-based	531	59.7	195	60.7	246	59.7	90	57.7	
Other	121	13.6	42	13.1	57	13.8	22	14.1	

Abbreviations: BC, breast cancer; BCS, breast-conserving surgery; HER2, human epidermal growth factor receptor 2; TTC, time to initiation of adjuvant chemotherapy.
**P* value from F test.
†Comorbidities evaluated included cardiac disease, vascular disease, diabetes mellitus, dyslipidemia, osteopenia/osteoporosis, connective tissue disorder, infectious diseases, and other.

Table 2. Survival Estimates for OS, RFS, and DRFS According to Patient Characteristics Among Patients With Stage I to III BC Diagnosed Between 1997 and 2011 and Treated With Adjuvant Chemotherapy

Characteristic	No. of Patients	No. of Events	5-Year OS	95% CI	*P*	No. of Events	5-Year RFS	95% CI	*P*	No. of Events	5-Year DRFS	95% CI	*P*
All patients	6,827	1,437	0.84	0.83 to 0.85		2,135	0.69	0.67 to 0.70		1,924	0.72	0.71 to 0.73	.74
TTC, days					.54				.67				.49
≤ 30	2,716	553	0.85	0.83 to 0.86		839	0.69	0.67 to 0.71		756	0.73	0.71 to 0.75	
31-60	2,994	634	0.83	0.82 to 0.85		930	0.69	0.67 to 0.71		833	0.72	0.70 to 0.74	
≥ 61	1,117	250	0.83	0.81 to 0.86		366	0.68	0.65 to 0.71		335	0.71	0.68 to 0.74	
Race/ethnicity					< .001				.01				.017
White	4,927	1,065	0.84	0.83 to 0.85		1,608	0.68	0.66 to 0.69		1,452	0.71	0.70 to 0.73	
African American	646	172	0.80	0.76 to 0.84		207	0.68	0.63 to 0.72		186	0.70	0.66 to 0.74	
Hispanic	912	160	0.86	0.83 to 0.89		230	0.74	0.71 to 0.77		206	0.77	0.74 to 0.8	
Other	342	40	0.90	0.85 to 0.93		90	0.74	0.68 to 0.79		80	0.78	0.72 to 0.83	
Pathologic tumor size					< .001				< .001				< .001
T1	3,643	533	0.90	0.89 to 0.91		813	0.78	0.76 to 0.80		702	0.82	0.80 to 0.83	
T2	2,642	715	0.78	0.76 to 0.80		1,069	0.59	0.57 to 0.61		989	0.62	0.60 to 0.64	
T3-4	448	156	0.70	0.65 to 0.75		198	0.50	0.45 to 0.56		184	0.54	0.48 to 0.60	
Pathologic nodal status					< .001				< .001				< .001
N0	2,804	429	0.88	0.86 to 0.89		672	0.76	0.74 to 0.78		574	0.79	0.78 to 0.81	
N1	2,539	485	0.86	0.85 to 0.88		757	0.70	0.68 to 0.72		686	0.74	0.72 to 0.76	
N2	872	265	0.78	0.75 to 0.81		368	0.57	0.53 to 0.61		346	0.60	0.56 to 0.64	
N3	506	221	0.66	0.61 to 0.71		275	0.47	0.42 to 0.52		262	0.50	0.45 to 0.55	
Breast cancer subtype					< .001				< .001				< .001
Hormone receptor–positive	3,834	604	0.88	0.87 to 0.90		1,005	0.73	0.72 to 0.75		921	0.76	0.75 to 0.78	
HER2-positive	1,142	261	0.81	0.78 to 0.84		368	0.64	0.61 to 0.68		333	0.68	0.65 to 0.71	
Triple-negative	889	299	0.65	0.61 to 0.68		371	0.54	0.50 to 0.58		324	0.59	0.55 to 0.62	
Nuclear grade					< .001				< .001				< .001
I, II	2,831	387	0.93	0.92 to 0.94		619	0.80	0.78 to 0.82		571	0.82	0.80 to 0.84	
III	3,671	967	0.77	0.75 to 0.78		1,335	0.61	0.59 to 0.63		1,190	0.65	0.63 to 0.67	
Lymphovascular invasion					< .001				< .001				< .001
Negative	4,600	810	0.88	0.87 to 0.89		1,261	0.73	0.72 to 0.75		1,131	0.77	0.75 to 0.78	
Positive	2,227	627	0.76	0.74 to 0.78		874	0.59	0.57 to 0.61		793	0.63	0.61 to 0.66	
Type of surgery					< .001				< .001				< .001
BCS	3,042	497	0.87	0.85 to 0.88		760	0.75	0.74 to 0.77		671	0.78	0.76 to 0.80	
Mastectomy	3,784	940	0.82	0.80 to 0.83		1,374	0.64	0.62 to 0.65		1,253	0.68	0.66 to 0.69	
No. of comorbidities					< .001				< .001				< .001
0	2,142	279	0.80	0.77 to 0.82		779	0.45	0.42 to 0.49		697	0.52	0.49 to 0.56	
1-2	2,970	728	0.85	0.84 to 0.87		845	0.74	0.73 to 0.76		764	0.77	0.75 to 0.79	
3-4	1,387	356	0.83	0.81 to 0.85		413	0.72	0.69 to 0.74		374	0.75	0.72 to 0.77	
≥ 5	328	74	0.87	0.82 to 0.9		98	0.72	0.67 to 0.77		89	0.75	0.70 to 0.80	
Hormone receptor–positive patients	3,834	604	0.88	0.87 to 0.90		1,005	0.73	0.72 to 0.75		921	0.76	0.75 to 0.78	
TTC, days					.39				.70				.54
≤ 30	1,604	243	0.89	0.87 to 0.91		410	0.74	0.71 to 0.76		372	0.77	0.74 to 0.79	
31-60	1,646	263	0.88	0.86 to 0.90		441	0.73	0.71 to 0.76		408	0.76	0.73 to 0.78	
≥ 61	584	98	0.87	0.83 to 0.90		154	0.73	0.68 to 0.77		141	0.75	0.71 to 0.79	

(continued on following page)

Table 2. Survival Estimates for OS, RFS, and DRFS According to Patient Characteristics Among Patients With Stage I to III BC Diagnosed Between 1997 and 2011 and Treated With Adjuvant Chemotherapy (continued)

Characteristic	No. of Patients	No. of Events	5-Year OS	95% CI	*P*	No. of Events	5-Year RFS	95% CI	*P*	No. of Events	5-Year DRFS	95% CI	*P*
HER2-positive patients	1,142	261	0.81	0.78 to 0.84		368	0.64	0.61 to 0.68		333	0.68	0.65 to 0.71	
TTC, days					.58				.46				.62
≤ 30	445	103	0.82	0.77 to 0.85		145	0.64	0.59 to 0.69		130	0.69	0.63 to 0.74	
31-60	493	106	0.82	0.77 to 0.86		152	0.66	0.60 to 0.70		139	0.69	0.63 to 0.73	
≥ 61	204	52	0.78	0.70 to 0.84		71	0.61	0.53 to 0.69		64	0.64	0.55 to 0.71	
HER2-positive patients treated with trastuzumab	591	53	0.85	0.81 to 0.89		92	0.77	0.71 to 0.81		84	0.78	0.73 to 0.83	
TTC, days					.01				.37				.24
≤ 30	233	19	0.88	0.81 to 0.93		35	0.80	0.72 to 0.86		34	0.82	0.74 to 0.87	
31-60	253	17	0.87	0.79 to 0.92		37	0.75	0.66 to 0.82		31	0.78	0.69 to 0.85	
≥ 61	105	17	0.75	0.61 to 0.85		20	0.72	0.59 to 0.82		19	0.7	0.56 to 0.81	
Triple-negative patients	889	299	0.65	0.61 to 0.68		371	0.54	0.5 to 0.58		324	0.59	0.55 to 0.62	
TTC, days					.004				.51				.55
≤ 30	321	92	0.70	0.64 to 0.76		131	0.56	0.50 to 0.62		114	0.61	0.55 to 0.67	
31-60	412	151	0.59	0.53 to 0.65		174	0.52	0.47 to 0.58		149	0.57	0.52 to 0.63	
≥ 61	156	56	0.67	0.57 to 0.75		66	0.53	0.44 to 0.61		61	0.56	0.47 to 0.65	

Abbreviations: BC, breast cancer; BCS, breast-conserving surgery; DRFS, distant relapse-free survival; HER2, human epidermal growth factor receptor 2; OS, overall survival; RFS, relapse-free survival; TTC, time to initiation of adjuvant chemotherapy.

Table 3. Multivariable Cox Proportional Hazards Model According to Stage and BC Subtypes Among 6,827 Patients With Stage I to III BC Diagnosed Between 1997 and 2011 and Treated With Adjuvant Chemotherapy

	OS			RFS			DRFS		
TTC (days)	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
All									
31-60 *v* ≤ 30	1.05	0.94 to 1.18	.39	1.04	0.94 to 1.14	.44	1.04	0.94 to 1.15	.49
≥ 61 *v* ≤ 30	1.19	1.02 to 1.38	.03	1.10	0.97 to 1.25	.15	1.13	0.99 to 1.29	.07
Stage I									
31-60 *v* ≤ 30	0.85	0.64 to 1.12	.25	0.89	0.71 to 1.12	.33	0.88	0.69 to 1.13	.31
≥ 61 *v* ≤ 30	0.80	0.54 to 1.18	.26	0.82	0.6 to 1.12	.20	0.81	0.57 to 1.14	.22
Stage II									
31-60 *v* ≤ 30	1.13	0.97 to 1.31	.12	1.16	1.02 to 1.31	.02	1.18	1.03 to 1.34	.02
≥ 61 *v* ≤ 30	1.17	0.96 to 1.42	.12	1.16	0.99 to 1.36	.07	1.20	1.02 to 1.43	.03
Stage III									
31-60 *v* ≤ 30	1.14	0.88 to 1.48	.33	0.99	0.8 to 1.23	.95	0.96	0.77 to 1.2	.7
≥ 61 *v* ≤ 30	1.76	1.26 to 2.46	< .001	1.34	1.01 to 1.76	.04	1.36	1.02 to 1.8	.03
Hormone receptor–positive									
31-60 *v* ≤ 30	1.14	0.95 to 1.36	.16	1.15	1.00 to 1.32	.04	1.18	1.02 to 1.36	.03
≥ 61 *v* ≤ 30	1.29	1.02 to 1.64	.03	1.14	0.94 to 1.37	.19	1.17	0.96 to 1.42	.12
HER2-positive									
31-60 *v* ≤ 30	0.92	0.69 to 1.22	.54	0.82	0.64 to 1.04	.1	0.85	0.66 to 1.09	.21
≥ 61 *v* ≤ 30	1.16	0.82 to 0.63	.41	1.02	0.76 to 1.38	.87	1.04	0.76 to 1.41	.82
Triple negative									
31-60 *v* ≤ 30	1.74	1.32 to 2.29	< .001	1.21	0.96 to 1.54	.11	1.23	0.95 to 1.59	.11
≥ 61 *v* ≤ 30	1.54	1.09 to 2.18	.02	1.24	0.91 to 1.68	.18	1.36	0.99 to 1.89	.06

NOTE. Variables in the model include age, race/ethnicity, axillary node involvement, tumor size, tumor grade, surgery, lymphovascular invasion, and No. of comorbidities (0, 1-2, 3-4, 5+). Among patients with triple-negative BC, type of chemotherapy was included as a different covariate. Among HER2-positive patients, the use of trastuzumab was included as an additional covariate.

Abbreviations: BC, breast cancer; DRFS, distant relapse-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival; TTC, time to initiation of adjuvant chemotherapy.

(HR, 1.19; 95% CI, 1.02 to 1.38) compared with patients who received adjuvant treatment ≤ 30 days after surgery. Among patients with stage I, there was no significant association between outcome and TTC. Patients with stage II disease experienced 18% and 20% increases in the risk of DRFS when systemic treatment started 31 to 60 days (HR, 1.18; 95% CI, 1.03 to 1.34) and ≥ 61 days (HR, 1.20; 95% CI, 1.02 to 1.43) from surgery. Among patients with stage III disease, those who started treatment ≥ 61 days from surgery had a 76% increase in the risk of death (HR, 1.76; 95% CI, 1.26 to 2.46), a 34% increase in the risk of relapse (HR, 1.34; 95% CI, 1.01 to 1.76), and a 36% increase in the risk of distant relapse (HR, 1.36; 95% CI, 1.02 to 1.80) compared with the patients who initiated adjuvant chemotherapy ≤ 30 days after surgery.

The effect that TTC had in outcomes was different according to BC subtype. Among patients with hormone receptor–positive tumors, those who received chemotherapy ≥ 61 days from surgery had a 29% increased risk of death (HR, 1.29; 95% CI, 1.02 to 1.64). Patients who received chemotherapy between 31 and 60 days after surgery had 15% (HR, 1.15; 95% CI, 1.00 to 1.32) and 18% (HR, 1.18; 95% CI, 1.02 to 1.36) increased risks of relapse and distant relapse, respectively, when compared with those who received chemotherapy ≤ 30 days after surgery. Patients with TNBC who received chemotherapy 31 to 60 days and ≥ 61 days after surgery had 74% (HR, 1.74; 95% CI, 1.32 to 2.29) and 54% (HR, 1.54; 95% CI, 1.09 to 2.18) increased risks of death compared with those who initiated chemotherapy ≤ 30 days from surgery. No differences were seen in RFS or DRFS.

We performed separate multivariable analysis among patients with HER2-positive tumors, categorizing them as trastuzumab treated (n = 591) and not trastuzumab treated (n = 551). The results are provided in Table 4. Among patients not treated with trastuzumab, the TTC had no impact on any of the evaluated outcome measures. However, trastuzumab-treated patients experienced a statistically significant increase in the risk of death when adjuvant chemotherapy was started ≥ 61 days after surgery compared with those who were treated ≤ 30 days after surgery (HR, 3.09; 95% CI, 1.49 to 6.39). In this group, there was also a trend toward worse RFS (HR, 1.78; 95% CI, 0.90 to 3.21) and DRFS (HR, 1.72; 95% CI, 0.94 to 3.15).

DISCUSSION

In this large retrospective cohort, we observed that the TTC after definitive surgery might influence survival outcomes for specific patient subgroups according to stage at diagnosis and BC subtypes.

Our study suggests that patients with more advanced stages experience worse outcomes when initiation of adjuvant chemotherapy is delayed. Among patients with stage II disease, we identified a detrimental effect in RFS and DRFS when chemotherapy started ≥ 61 days after definitive surgery with no impact on OS. Among patients with stage III BC, a delay in initiation of chemotherapy of ≥ 61 days was associated with a detrimental effect in RFS, DRFS, and OS.

It is well known that tumor size and lymph node involvement status are important factors associated with risk of recurrence and mortality among patients with BC.[16] Larger tumors are associated with worst RFS and OS, even in the absence of lymph node involvement.[17,18] In addition, among patients with advanced stages, the presence of pre-existing micrometastatic disease is more likely, making our results biologically plausible.

Delays in treatment initiation have been reported to be more likely to occur in Medicare patients, in low-income populations, and in racial minorities.[19] A recent noninterventional study that retrospectively evaluated a cohort of 1,786 low-income patients with BC from North Carolina[20] reported that among patients with late-stage disease (defined as regional or distant), a delay of ≥ 60 days between diagnosis and first treatment was associated with worse OS (HR, 1.66; 95% CI, 1.00 to 2.77) and worse BC-specific survival (HR, 1.85; 95% CI, 1.04 to 3.27). Among patients with early BC (defined as in situ or local disease), a delay in initiation of treatment was not associated with worse outcome. This findings are consistent with our study, in which patients with more advanced stage at diagnosis experienced worse RFS and OS with delayed TTC.

Our study includes one of the largest single-institution cohorts of patients evaluating TTC and BC outcomes. A recent meta-analysis that included data on 15,327 patients reported that each 4-week delay in the initiation of adjuvant chemotherapy resulted in a 6% increase in the risk of death (HR, 1.06; 95% CI, 1.02 to 1.10) and an 8% increase in the risk of relapse (HR, 1.08; 95% CI, 1.03 to 1.14).[15] Previously, an analysis of the Breast Cancer Study Group (IBCSG) Trials I, II, and VI showed that in premenopausal patients with node-positive and hormone receptor–negative tumors, 10-year disease-free survival was 60% for patients who started chemotherapy within 20 days and 34% for those who started adjuvant chemotherapy 21 to 86 days after surgery. Interestingly, early initiation of chemotherapy had no impact among patients with hormone receptor–positive tumors, but it did have a positive effect in those patients with hormone receptor–negative disease.[10] Similarly, in our study, a delay in the TTC was associated with worse outcomes among patients with TNBC, suggesting that delaying the initiation of adjuvant chemotherapy could be detrimental for patients with BC subtypes that are typically recognized as having higher proliferation and more aggressive behavior.

Among patients with hormone receptor–positive tumors, there was a detrimental impact on survival for those starting chemotherapy ≥ 61 days and worse RFS and DRFS for those treated between 31 and 60 days after surgery; however, the magnitude of the risk was much smaller than when evaluating TNBC or trastuzumab-treated HER2-positive patients. Our results are consistent with the majority of retrospective studies that have addressed this issue. Numerous trials have demonstrated that the magnitude of benefit of adjuvant chemotherapy is less pronounced among hormone receptor–positive patients.[21] In addition, tamoxifen[2] and aromatase inhibitors[22-24] are important and effective therapeutic agents that, when used in the adjuvant setting, reduce the risk of death and recurrence. It is possible that the detrimental effect observed associated with delayed TTC among patients with hormone receptor–positive tumors is related to a delay in the initiation of endocrine therapy.

The group of patients with HER2-positive tumors that received trastuzumab-based therapy experienced an important increase in the risk of death when systemic treatment was initiated ≥ 61 days after surgery compared with those whose treatment started ≤ 30 days after surgery. The HER2 overexpression or amplification in primary tumors is associated with worse prognosis in untreated patients and might also correlate with other factors associated with poor prognosis, such as tumor grade and nodal status.[25-27] Trastuzumab-based chemotherapy is recognized as a key component of the adjuvant treatment and is part of the standard of care for patients with HER2-positive

Table 4. Multivariable Cox Proportional Hazards Model for Patients With HER2-Positive BC (n = 1,142) According to Trastuzumab-Based Therapy Who Were Diagnosed With Stage I to III BC Between 1997 and 2011 and Were Treated With Adjuvant Chemotherapy

	OS			RFS			DRFS		
TTC (days)	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Patients treated with trastuzumab (n = 591)									
31-60 *v* 0-30	0.74	0.35 to 1.54	.41	0.98	0.6 to 1.62	.95	0.81	0.48 to 1.38	.44
61+ *v* 0-30	3.09	1.49 to 6.39	.002	1.78	0.99 to 3.21	.06	1.72	0.94 to 3.15	.08
Patients not treated with trastuzumab (n = 551)									
31-60 *v* 0-30	1.04	0.76 to 1.42	.82	0.84	0.63 to 1.11	.22	0.94	0.7 to 1.26	.66
61+ *v* 0-30	0.86	0.57 to 1.29	.46	0.92	0.65 to 1.3	.65	0.94	0.65 to 1.36	.73

NOTE. Variables in the model include age, race/ethnicity, axillary node involvement, tumor size, tumor grade, surgery, lymphovascular invasion, and number of comorbidities (0, 1-2, 3-4, 5+).
Abbreviations: BC, breast cancer; DRFS, distant relapse-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival; TTC, time to initiation of adjuvant chemotherapy.

tumors.[28-31] Similarly, the TNBC subgroup experienced a detrimental effect in delaying initiation of adjuvant chemotherapy in terms of OS, with a 74% and 54% increased risk of death for those women who received chemotherapy 31 to 60 days and ≥ 61 days after definitive surgery, respectively. TNBC is known to have a more aggressive behavior when compared with other BC subtypes.[32] It is important to mention that there is a lack of targeted therapies for this patient population and that chemotherapy is the only effective known treatment. The great benefit of adjuvant systemic chemotherapy in this subgroup of patients is well established and disproportionately greater when compared with patients with hormone receptor–positive BC.[33] The results of our study strongly suggest that early initiation of adjuvant chemotherapy should be favored.

Despite our interesting findings, our study has some limitations related to its retrospective nature. We believe that our results, although obtained from a retrospective analysis, are important because clinical trials designed to answer this question would be unethical. The only prospective trial that indirectly addressed this matter compared whether the sequence of administration of chemotherapy and radiation therapy after breast-conserving surgery had an impact on outcome among patients with early-stage BC. In a study by Recht et al,[34] local BC recurrences were more common when radiation therapy was given after the completion of chemotherapy, whereas systemic recurrence was more frequent when radiation therapy was given before chemotherapy. However, the updated analysis did not demonstrate any difference in terms of the pattern of recurrence and survival between the two groups.[35]

Other limitations of our study include the lack of a group of patients who did not receive chemotherapy and the small number of patients with stage III cancer, since most of these patients received neoadjuvant chemotherapy at our institution. In our population, 84.5% of the patients had stage I or II BC, which represents a group of patients at lower risk of BC recurrence.[36,37] Despite our median follow-up of 59.3 months, it is possible that longer follow-up is needed, particularly to evaluate the effect of delay in adjuvant chemotherapy initiation among patients with hormone receptor–positive BC. In addition, among hormone receptor–positive patients, duration of or compliance with adjuvant endocrine therapy was not evaluated.

In clinical practice, many factors can influence the time interval between surgery and initiation of chemotherapy. Some of the frequently involved factors are related to patients' clinical condition and comorbidities. In our multivariable analysis, we adjusted for important comorbidities; however, some degree of residual confounding cannot be completely excluded.

It is not clear why we observed a detrimental effect on OS among patients with trastuzumab-treated HER2-positive and TNBC tumors who delayed the initiation of chemotherapy without worse RFS or DRFS. A relationship between the factors that determine a delay in TTC and survival cannot be excluded, and caution in the interpretation of our data is warranted.

In conclusion, we demonstrated that delaying the initiation of adjuvant chemotherapy was associated with worse BC survival outcomes and that the clinical impact varies according to the stage and the BC subtype. Early initiation of adjuvant chemotherapy is particularly relevant for patients with advanced-stage BC at diagnosis, and those with TNBC and trastuzumab-treated HER2-positive tumors. The adverse outcomes occurred when chemotherapy was delayed ≥ 61 days, which in most circumstances, gives medical oncologists enough time to initiate adjuvant chemotherapy. Among patients with stage II and III BC, TNBC, and HER2-positive tumors, every effort should be made to avoid postponing the initiation of adjuvant chemotherapy. This may lead to an improvement in outcomes for these subsets of patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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GLOSSARY TERMS

American Joint Committee on Cancer (AJCC)/ International Union Against Cancer (UICC) TNM staging: a cancer staging system that describes the extent of cancer in a patient's body. "T" describes the size of the tumor and whether it has invaded nearby tissue; "N" describes regional lymph nodes that are involved; "M" describes distant metastasis (spread of cancer from one body part to another). The TNM Classification of Malignant Tumours was developed and maintained by the UICC to achieve consensus on one globally recognized standard for classifying the extent of spread of cancer. The TNM classification was also used by the AJCC. In 1987, the UICC and AJCC staging systems were unified into a single staging system. Prognosis of a patient is defined by TNM classification.

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

estrogen receptor (ER): ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ERα and ERβ). ERα is one of the most important proteins controlling breast cancer function. ERβ is present in much lower levels in breast cancer, and its function is uncertain. Estrogen receptor status guides therapeutic decisions in breast cancer.

HER2/neu (human epidermal growth factor receptor 2): also called ErbB2. HER2/neu belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

progesterone receptor (PgR): nuclear proteins that are activated by the hormone progesterone in breast cancer cells that are hormone-dependent. See estrogen receptor (ER).

trastuzumab: a humanized anti-ErbB2 monoclonal antibody approved for treating patients whose breast cancers overexpress the ErbB2 protein or demonstrate ErbB2 gene amplification. It is currently being tested in combination with other therapies.

triple-negative phenotype: breast tumors that are negative for progesterone and estrogen and that underexpress HER2.

