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Association Between Time to Operation and Pathologic Stage in Ductal Carcinoma in Situ and Early-Stage Hormone Receptor-Positive Breast Cancer

Christina A Minami, MD, MS, Olga Kantor, MD, MS, Anna Weiss, MD, Faina Nakhlis, MD, FACS, Tari A King, MD, FACS, Elizabeth A Mittendorf, MD, PhD, FACS

BACKGROUND: During the COVID-19 pandemic, surgical delays have been common for patients with ductal carcinoma in situ (DCIS) and early-stage estrogen receptor-positive (ER+) breast cancer, often in favor of neoadjuvant endocrine therapy (NET). To understand possible ramifications of these delays, we examined the association between time to operation and pathologic staging and overall survival (OS).

STUDY DESIGN: Patients with DCIS or ER+ cT1-2N0 breast cancer treated from 2010 through 2016 were identified in the National Cancer Database. Time to operation was recorded. Factors associated with pathologic upstaging were examined using logistic regression analyses. Cox proportional hazard models were used to analyze OS. Analyses were stratified by disease stage and initial treatment strategy.

RESULTS: There were 378,839 patients identified. Among those undergoing primary surgical procedure, time to operation was within 120 days in > 98% in all groups. Among cT1-2N0 patients selected for NET, operations were performed within 120 days in 59.6% of cT1N0 and 30.9% of cT2N0 patients. Increased time to operation was associated with increased odds of pathologic upstaging in DCIS patients (ER+: 60 to 120 days: odds ratio 1.15; 95% CI, 1.08 to 1.22; more than 120 days: odds ratio 1.44; 95% CI, 1.24 to 1.68; ER−: 60 to 120 days: NS; more than 120 days: odds ratio 1.36; 95% CI, 1.01 to 1.82; 60 days or less: reference), but not in patients with invasive cancer, irrespective of initial treatment strategy. No difference in OS was seen by time to operation in DCIS or NET patients.

CONCLUSIONS: Increased time to operation was associated with a small increase in pathologic upstaging in DCIS patients, but did not impact OS. In patients with cT1-2N0 disease, NET use did not impact stage or OS, supporting the safety of delay strategies in ER+ breast cancer patients during the pandemic. (J Am Coll Surg 2020;231:434−447. © 2020 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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From the Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, and Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA.

Correspondence address: Elizabeth A Mittendorf, MD, PhD, FACS, Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, and Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, 450 Brookline Ave, Yawkey 1220, Boston, MA 02215. email: emittendorf@bwh.harvard.edu

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Abbreviations and Acronyms

BCS = breast-conserving surgery
DCIS = ductal carcinoma in situ
ER = estrogen receptor
NCDB = National Cancer Database
NET = neoadjuvant endocrine therapy
OR = odds ratio
OS = overall survival

To minimize patient exposure and preserve hospital resources during the COVID-19 pandemic, hospitals across the US were asked to sharply decrease the volume of nonurgent surgical cases, including oncologic procedures. The COVID-19 Pandemic Breast Cancer Consortium released recommendations about prioritization of breast cancer operations to aid decision-making, with the recognition that few prospective data existed on the repercussions of the suggested strategies.[1] It was recommended that operations for ductal carcinoma in situ (DCIS) be deferred until after resolution of the pandemic, with suggested initiation of neoadjuvant endocrine therapy (NET) in patients with estrogen receptor-positive (ER+) DCIS. NET was similarly recommended as the preferred strategy for patients with early-stage ER+ invasive breast cancer.

The impact of time to operation on breast cancer outcomes in these very-early-stage patients remains unclear. Time to operation has been shown to be associated with increase in upstaging from DCIS to invasive disease on the order of 1% per month, but with excellent survival rates even in upstaged patients.[2] In invasive cancer patients, studies using nodal positivity as a surrogate outcomes measure have demonstrated mixed results.[3,4] In addition, survival analyses have similarly reported varied findings, leaving surgeons without a clear sense of the repercussions that can result from treatment delays.

NET use has primarily been used in patients with stage II and III ER+ disease, demonstrating tumor responses comparable with those seen with neoadjuvant chemotherapy.[5,6] Survival data in NET patients are more difficult to interpret, not only because of the long disease-free intervals associated with ER+ disease, but also because adjuvant treatment pathways are not standardized in NET patients.[5,7] There are definitive data in older adults with ER+ disease that demonstrate no overall survival (OS) difference between primary endocrine therapy alone vs operation plus endocrine therapy.[8-10] Use of NET as a delay strategy during the pandemic in patients with early-stage ER+ disease has a basis in high-quality evidence, but given the historical selection bias for NET in postmenopausal patients, it does to a certain extent represent an extrapolation of existing data to a broader population.

The true oncologic ramifications of these delay strategies will be observed over time. Understanding the possible outcomes earlier, however, could be useful in effectively counseling and reassuring patients about surgical delays and the broadened use of NET. Our primary objective was to understand the possible effects of COVID-related surgical delays on breast oncology outcomes by examining the association between time to operation and pathologic staging, with secondary analyses evaluating OS and extent of breast operation.

METHODS

Data from 2010 through 2016 were abstracted from the participant user file of the National Cancer Database (NCDB). The NCDB is an oncology dataset that captures approximately 70% of newly diagnosed cancer in the US.[1] It is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons, receiving data from approximately 1,500 Commission on Cancer-accredited cancer programs. This study was deemed exempt from review by the Brigham and Women's Hospital IRB.

Patients

All patients diagnosed January 1, 2010 through December 31, 2016 who underwent breast cancer operations were identified. Given recommendations of the

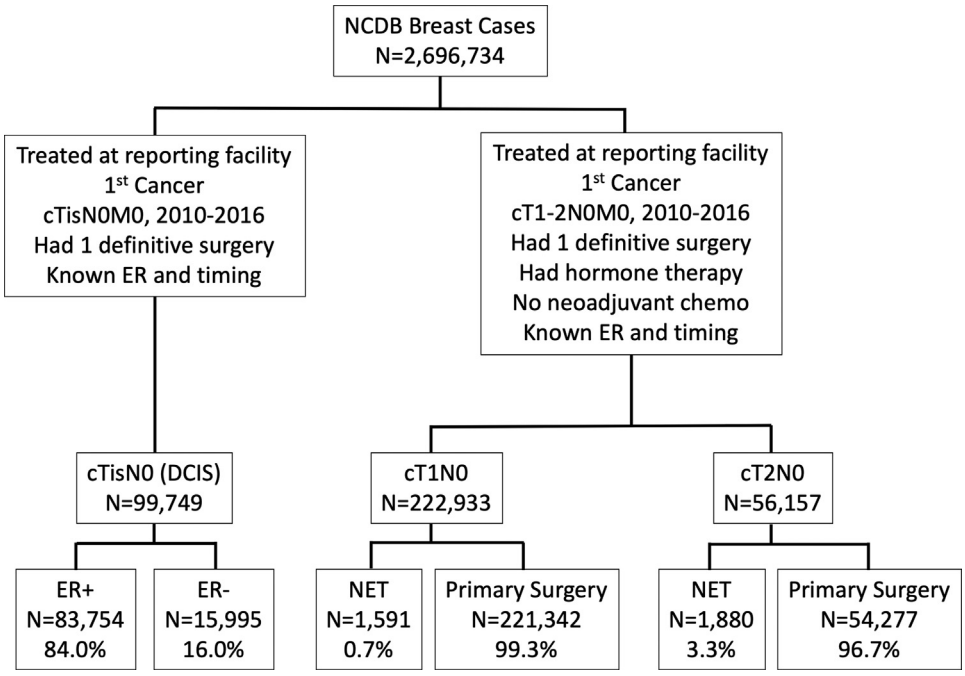

Figure 1. Consolidated Standards of Reporting Trials diagram. ER, estrogen receptor; NCDB, National Cancer Database; NET, neoadjuvant endocrine therapy.

COVID-19 Pandemic Breast Cancer Consortium, the population of interest was patients with DCIS or early-stage (cT1-2N0) ER+ disease.[1] Patients who were treated outside the reporting facility, had unknown ER status, unknown surgical timing, unknown surgical pathology data, or who underwent more than 1 operation were excluded. In addition, patients who did not undergo operation within 1 year of diagnosis, who received neoadjuvant chemotherapy, or, in the case of patients with invasive disease, those who did not receive endocrine therapy at all were excluded. An exceedingly small number of patients with DCIS received NET, precluding reliable analysis of this subpopulation, and were excluded. The remaining 99,749 DCIS patients, 222,933 cT1N0, and 56,157 cT2N0 patients were assessed (Fig. 1).

Variables

The exposure of interest was time to operation from time of diagnosis, originally defined as 30 or fewer days, 31 to 60 days, 61 to 90 days, 91 to 120 days, and more than 120 days. As outcomes of interest did not significantly vary from 0 to 30 vs 30 to 60 days or from 60 to 90 vs 90 to 120 days, these categories were collapsed into 60 or fewer days, 61 to 120 days, and more than 120 days. Patient-level variables included age (18 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, and older than 80 years), race/ethnicity (white, black, Hispanic, Asian, and other/unknown), insurance status (private, Medicare, Medicaid, uninsured, and other/unknown), regional location of the patient's home ZIP code (metropolitan, urban, or rural). Disease characteristics included tumor grade (classified as 1, 2, or 3) and tumor histology (ductal, lobular, or mixed). Both clinical and pathologic tumor category (Tis, T1, T2, T3, or T4) and nodal category (Nx, N0, N1, N2, or N3) were included. Treatment characteristics included operation type (breast-conserving surgery [BCS] vs mastectomy), radiation therapy (yes/no), and adjuvant chemotherapy (yes/no). Facility type was also incorporated, defined by Commission on Cancer accreditation status as a community cancer program, comprehensive community cancer program, academic/research program, or integrated network cancer program.

Outcomes measures

The main measure of interest was the proportion of DCIS, cT1N0, and cT2N0 patients who were upstaged on final surgical pathology. Inclusion criteria were based on T and N categories, and the outcomes measure was based on the 8th edition of the American Joint Committee on Cancer's *AJCC Cancer Staging Manual*.[11] Patients included in the cT1N0 and cT2N0 groups were recoded by the 8th edition clinical prognostic staging criteria and were deemed "upstaged" if their pathologic prognostic stage was higher than their clinical prognostic stage.

Table 1. Patient Characteristics

	DCIS patient				cT1N0 patient				cT2N0 patient			
	ER+ (n = 83,754)		ER− (n = 15,995)		NET (n = 1,591)		Primary operation (n = 221,342)		NET (n = 1,880)		Primary operation (n = 54,277)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age*												
18–39 y	2,451	2.9	507	3.2	29	1.8	4,818	2.2	21	1.1	2,671	4.9
40–49 y	17,150	20.5	2,331	14.6	170	10.7	30,432	13.7	157	8.4	9,827	18.1
50–59 y	23,593	28.2	4,661	29.1	336	21.1	55,485	25.1	362	19.3	13,327	24.6
60–69 y	23,972	28.6	48,890	30.6	492	30.9	72,239	32.6	581	30.9	14,621	26.9
70–79 y	13,045	15.6	2,657	16.6	357	22.4	45,174	20.4	449	23.9	9,223	17.0
80 y or older	3,543	4.2	949	5.9	207	13.0	13,194	6.0	310	16.5	4,608	8.5
Race*												
White	63,659	76.0	12,551	78.5	1,322	83.1	186,587	84.3	1,491	79.3	43,628	80.4
Black	10,665	12.7	1,643	10.3	119	7.5	16,254	7.3	171	9.1	4,829	8.9
Hispanic	5,073	6.1	947	5.9	93	5.8	10,278	4.6	137	7.3	3,232	6.0
Asian	3,859	4.6	767	4.8	47	3.0	6,961	3.1	70	3.7	2,240	4.1
Other	498	0.6	87	0.5	10	0.6	1,262	0.6	11	0.6	348	0.6
Comorbidity index												
0	70,824	84.6	13,514	84.5	1,234	77.6	184,373	83.3	1,539	81.9	44,446	81.9
1	10,519	12.6	1,982	12.4	239	15.0	29,636	13.4	241	12.8	7,757	14.3
2	1,853	2.2	391	2.4	78	4.9	5,549	2.5	68	3.6	1,524	2.8
≥ 3	558	0.7	108	0.7	40	2.5	1,784	0.8	32	1.7	550	1.0
Insurance*												
Private	50,754	60.6	9,193	57.5	663	41.7	117,865	53.3	713	37.9	29,021	53.5
Medicare	25,778	30.8	5,426	33.9	756	47.5	86,475	39.1	953	50.7	19,431	35.8
Medicaid	4,228	5.0	789	4.9	102	6.4	10,099	4.6	120	6.4	3,679	6.8
Other government	931	1.1	167	1.0	12	0.8	2,233	1.0	20	1.1	577	1.1
Uninsured	1,225	1.5	260	1.6	27	1.7	2,603	1.2	43	2.3	1,016	1.9
Unknown	838	1.0	160	1.0	31	1.9	2,067	0.9	31	1.6	553	1.0
Region												
Metro	70,858	84.6	13,422	83.9	1,296	81.5	182,504	82.5	1,571	83.6	44,633	82.2
Urban	9,558	11.4	1,902	11.9	218	13.7	29,281	13.2	226	12.0	7,372	13.6
Rural	1,214	1.4	257	1.6	33	2.1	3,917	1.8	29	1.5	962	1.8
Unknown	2,124	2.5	414	2.6	44	2.8	5,640	2.5	54	2.9	1,310	2.4
Facility type*												
Community	6,465	8.0	1,183	7.6	112	7.2	19,278	8.9	132	7.1	4,757	9.2
Comprehensive	36,644	45.1	7,176	46.3	623	39.9	98,290	45.4	717	38.6	23,671	45.9
Academic	25,206	31.0	4,674	30.2	524	33.5	66,491	30.7	704	37.9	15,662	30.3
Integrated network	12,988	16.0	2,455	15.9	303	19.4	32,465	15.0	306	16.5	7,516	14.6
Histology*												
Ductal	NA	NA	NA	NA	1,219	76.6	176,972	80.0	1,284	68.3	39,905	73.5
Lobular	NA	NA	NA	NA	199	12.5	22,192	10.0	349	18.6	8,322	15.3
Mixed	NA	NA	NA	NA	173	10.9	22,178	10.0	247	13.1	6,050	11.1
Grade*												
1	11,314	13.5	263	1.6	591	27.1	77,878	35.2	498	26.5	8,971	16.5
2	33,311	39.8	2,149	13.4	805	50.6	109,108	49.3	1,040	55.3	28,762	53.0
3	26,257	31.4	10,903	68.2	124	7.8	25,837	11.7	267	14.2	14,529	26.8
Unknown	12,872	15.4	2,680	16.8	71	4.5	8,519	3.8	75	4.0	2,015	3.7

(Continued)

Table 1. Continued

	DCIS patient				cT1N0 patient				cT2N0 patient			
	ER+ (n = 83,754)		ER− (n = 15,995)		NET (n = 1,591)		Primary operation (n = 221,342)		NET (n = 1,880)		Primary operation (n = 54,277)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Operative time from diagnosis												
< 60 d	69,539	83.0	13,197	82.5	352	22.1	199,778	90.3	137	7.3	47,598	87.7
61−120 d	12,689	15.2	2,504	15.7	596	37.5	20,208	9.1	444	23.6	6,187	11.4
> 120 d	1,526	1.8	294	1.8	643	40.4	1,356	0.6	1,299	69.1	492	0.9
Operation type*												
BCS	60,120	71.8	9,402	58.8	1,085	68.2	170,933	77.2	1,173	62.4	26,803	49.4
Mastectomy	23,634	28.2	6,593	41.2	506	31.8	50,409	22.8	707	37.6	27,474	50.6
Axillary operation type*												
None	36,691	43.8	4,704	29.4	168	10.6	5,382	59.3	186	9.9	1,174	2.2
SLNB	22,360	26.7	5,766	36.0	916	57.6	131,306	11.5	952	50.6	25,783	47.5
SLNB/ALND	3,353	4.0	676	4.2	184	11.6	25,431	11.5	292	15.5	10,514	19.4
ALND	2,649	3.2	958	6.0	103	6.5	12,486	5.6	130	6.9	4,519	8.3
Unknown	18,701	22.3	3,891	24.3	220	13.8	46,737	21.1	320	17.0	12,287	22.6
pT*												
pT0	75,075	89.6	13,192	82.5	37	2.3	660	0.3	17	0.9	55	0.1
pT1	8,246	9.8	2,619	16.4	1,308	82.2	197,252	89.1	684	36.4	10,641	19.6
pT2	351	0.4	151	0.9	224	14.1	2,216	10.0	1,064	56.6	40,939	75.4
pT3	61	0.1	26	0.2	20	1.3	1,080	0.5	95	5.1	2,429	4.5
pT4	11	0.0	7	0.0	2	0.1	134	0.1	20	1.1	213	0.4
pN*												
pN0	58,328	69.6	12,539	78.4	1,182	74.3	184,293	83.3	1,138	60.5	34,653	63.8
pN1	840	1.0	285	1.8	247	15.5	30,129	13.6	501	26.6	15,301	28.2
pN2	64	0.1	39	0.2	21	1.3	2,422	1.1	60	3.2	2,617	4.8
pN3	37	0.0	12	0.1	9	0.6	695	0.3	30	1.6	886	1.6
pNx	24,485	29.2	3,120	19.5	132	8.3	3,803	1.7	151	8.0	820	1.5
Adjuvant treatment												
Endocrine therapy*	43,873	52.4	979	6.1	1,591	100	221,342	100	1,880	100	54,277	100
Chemotherapy*	1,767	2.1	1,177	7.4	177	11.1	39,749	18.0	284	15.6	23,139	42.6
Radiation*	45,565	54.4	8,157	51.0	849	53.4	161,328	72.9	1,052	56.0	326,680	60.2

*$p < 0.05$.

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; ER, estrogen receptor; NA, not applicable; NET, neoadjuvant endocrine therapy; pT, pathologic tumor category; pN, pathologic nodal category.

Secondary outcomes measures were 5-year OS and type of breast procedure (BCS vs mastectomy).

Statistical analysis

Time to operation was treated as a categorical variable, defined by the date of diagnosis to the date of operation. All tests were 2-sided with a p value < 0.05 considered statistically significant. Analyses were stratified by clinical staging on presentation (DCIS, cT1N0, cT2N0); all DCIS patients (ER+ and ER−) underwent upfront operation, and the cT1N0 and cT2N0 groups were also stratified by initial treatment strategy (NET vs primary operation). Chi-square tests of proportion were performed to test the significance of baseline differences in the study population. Univariable logistic regression models were used to examine factors associated with pathologic upstaging (eTable 1). To test the significance of time to operation controlled for all other patient and hospital covariates, a multivariable analysis was performed using a random intercept, fixed slope, logistic regression model with the hospital as a random effect. Variables for this model were chosen a priori, and included age, race, Charlson Comorbidity Index score, insurance status, facility type, tumor histology, operation type, and time to

Table 2. Patient Population by TNM Stage/Primary Treatment, American Joint Committee on Cancer 8th Edition Clinical Prognostic Staging and 8th Edition Pathologic Prognostic Staging

Cancer type, AJCC 8th edition clinical prognostic stage, pathologic prognostic stage	n	%	Pathologic upstaging
ER+ DCIS (n = 83,754)			
0			
0	75,024	89.6	Same stage
IA	5,561	6.6	Upstage
IB	252	0.3	Upstage
IIA-B	162	0.4	Upstage
IIIA-C	46	0.0	Upstage
Unknown	2,709	3.2	Upstage
ER− DCIS (n = 15,995)			
0			
0	13,175	82.4	Same stage
IA	922	5.8	Upstage
IB	590	3.6	Upstage
IIA-B	298	1.9	Upstage
IIIA-C	81	0.5	Upstage
Unknown	1,926	5.8	Upstage
cT1N0 NET (n = 1,395)			
IA	1,375	98.6	—
0	30	2.2	Downstage
IA	1,222	88.9	Same stage
IB	79	5.7	Upstage
IIA-B	33	2.4	Upstage
IIIA-C	11	0.8	Upstage
IB	20	1.4	—
0	0	0	Downstage
IA	8	40.0	Downstage
IB	0	0	Same stage
IIA-B	11	55.0	Upstage
IIIA-C	1	5.0	Upstage
cT1N0 upfront operation (n = 209,102)			
IA	204,944	98.0	—
0	587	0.3	Downstage
IA	189,159	92.3	Same stage
IB	10,740	5.2	Upstage
IIA-B	2,776	1.7	Upstage
IIIA-C	888	0.4	Upstage
IB	4,158	2.0	—
0	11	0.3	Downstage
IA	2,917	70.2	Downstage
IB	0	0	Same stage
IIA-B	1,125	27.1	Upstage
IIIA-C	106	2.5	Upstage
cT2N0 NET (n = 1,649)			
IB	1,288	78.1	—
0	11	0.9	Downstage
IA	1,019	79.1	Downstage

(Continued)

Table 2. Continued

Cancer type, AJCC 8th edition clinical prognostic stage, pathologic prognostic stage	n	%	Pathologic upstaging
IB	229	17.8	Same stage
IIA-B	0	0	Upstage
IIIA-C	29	2.3	Upstage
IIA	332	20.1	—
0	2	0.6	Downstage
IA	88	26.5	Downstage
IB	116	34.9	Downstage
IIA	79	23.8	Same stage
IIB	30	9.0	Upstage
IIIA-C	17	5.1	Upstage
IIB	29	1.8	—
0	0	0	Downstage
IA	8	27.6	Downstage
IB	0	0	Downstage
IIA	11	37.9	Downstage
IIB	7	24.1	Same stage
IIIA-C	3	10.3	Upstage
cT2N0 upfront operation (n = 51,208)			
IB	33,648	65.7	—
0	39	0.1	Downstage
IA	24,929	74.1	Downstage
IB	8,061	24.0	Same stage
IIA-B	0	0	Upstage
IIIA-C	619	1.8	Upstage
IIA	14,831	29.0	—
0	6	0.0	Downstage
IA	1,997	13.5	Downstage
IB	6,454	43.5	Downstage
IIA	4,396	29.6	Same stage
IIB	1,412	9.5	Upstage
IIIA-C	566	3.9	Upstage
IIB	2,729	5.3	—
0	4	0.1	Downstage
IA	285	1.0	Downstage
IB	0	0	Downstage
IIA	1,746	64.0	Downstage
IIB	520	19.1	Same stage
IIIA-C	174	6.4	Upstage

AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; NET, neoadjuvant endocrine therapy.

operation. Tumor grade was not included in this model, given that it is a significant part of the 8th edition prognostic pathologic staging system (ie the outcomes variable). A multivariable logistic regression model was also performed to determine significant factors associated with receipt of NET. Cox proportional hazards models—adjusted for age, race, comorbidity index, tumor grade, histology, operation type, pathologic tumor and nodal category, and adjuvant therapy (chemotherapy and radiation therapy)—were used to compare OS by time from diagnosis to operation by clinical disease stage (DCIS, cT1N0, cT2N0), and initial treatment strategy (NET vs primary operation). All analyses were performed using SPSS, version 19.0 (IBM Corp).

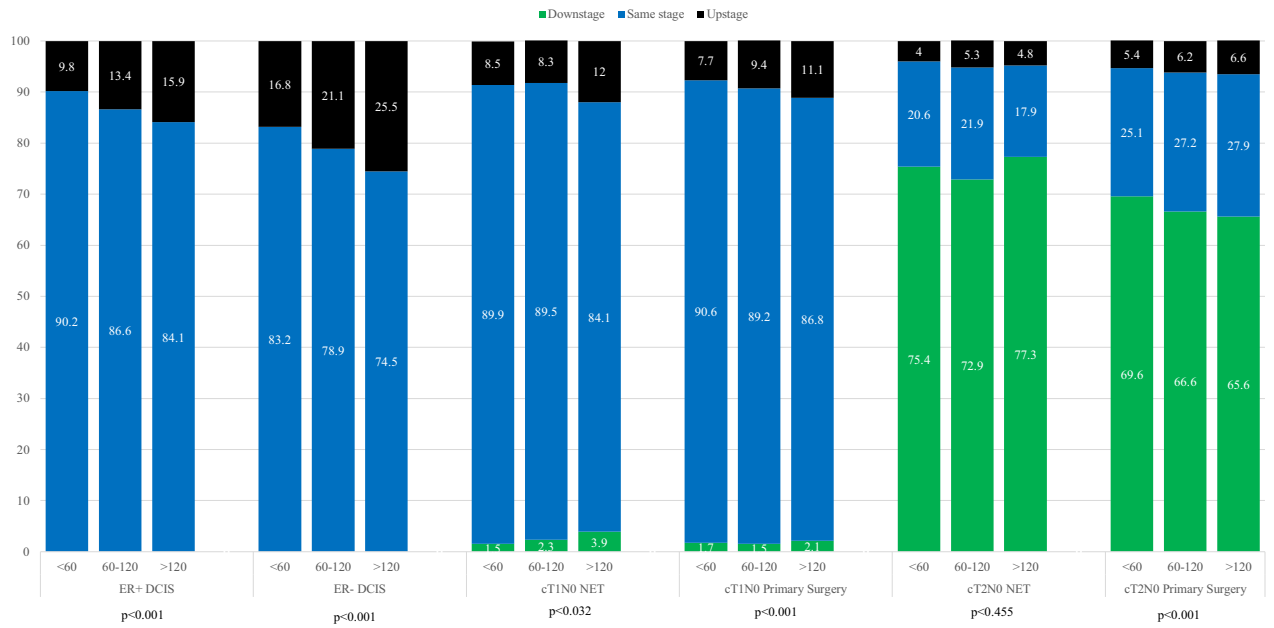

Figure 2. Change in American Joint Committee on Cancer 8th edition pathologic prognostic stage by time to operation, stratified by disease subtype and initial treatment strategy; time to operation in days. DCIS, ductal carcinoma in situ; ER, estrogen receptor; NET, neoadjuvant endocrine therapy.

RESULTS

Of the 99,749 DCIS patients, 83,754 (84%) had ER+ disease and 15,995 (16%) had ER− disease. Of the patients with cT1N0 disease, 1,591 (0.7%) underwent NET and the remaining underwent primary operation. A greater percentage of patients (3.3%) with cT2N0 disease underwent NET (n = 1,880). For patients with cT1-2N0 disease, multivariable analysis showed that older age, higher comorbidity index (Charlson Comorbidity Index score $\geq$ 3: odds ratio [OR] 1.83; 95% CI, 1.41 to 2.39 [reference: Charlson Comorbidity Index of 0]), lobular disease (OR 1.17; 95% CI, 1.06 to 1.29), and cT2 vs cT1 tumor (OR 5.40; 95% CI, 5.01 to 5.81) were among the factors significantly associated with NET receipt (eTable 2).

Clinicopathologic characteristics of the patients in each group are shown in Table 1. In the DCIS group, 98.2% of patients underwent operations in the first 120 days. Similarly, 99.4% of cT1N0 patients and 99.1% of cT2N0 patients in the primary operation group underwent operation within 120 days. In contrast, 59.6% of the cT1N0 and 30.9% of the cT2N0 NET patients underwent operations within 120 days.

Among DCIS patients, mastectomy was more common in ER− than ER+ disease (41.2% vs 28.2%; $p < 0.01$). Among cT1N0 patients, mastectomy was more common in the NET group (31.8%) than in the primary operation group (22.8%) ($p < 0.01$), and in cT2N0 patients, BCS rates were higher in the NET group compared with the primary operation group (62.4% vs 49.4% respectively; $p < 0.01$).

Association between time to operation and pathologic upstaging

In total, a greater proportion of patients with ER− DCIS (17.6%) were upstaged to invasive disease compared with patients with ER+ DCIS (10.4%) (Table 2). The proportion of patients who were upstaged on final pathology increased by time to operation among both the ER+ and ER− DCIS patients (Fig. 2; $p < 0.001$ for both). A small group of patients (< 5%) had invasive disease on final pathology but were missing elements (eg grade or nodal status) needed to accurately stage them per the 8th edition prognostic pathologic staging criteria, and were coded as being upstaged, yet "unknown." Among the statistically significant factors associated with pathologic upstaging among ER+ DCIS patients on adjusted analysis was time to operation, as patients undergoing operations more than 60 days after diagnosis had an OR of 1.15 (95% CI, 1.08 to 1.22) compared with those who underwent operations within the first 60 days (Table 3). Patients with ER− DCIS also had higher odds of being upstaged, but only if they underwent operations more than 120 days after diagnosis (OR 1.36; 95% CI, 1.01 to 1.82). Patients with both ER+ and ER− DCIS undergoing mastectomy were

Table 3. Multivariable Analysis of Factors Associated with Upgrade by the American Joint Committee on Cancer 8th Edition Prognostic Staging

Patient characteristic	ER+ DCIS		ER− DCIS		NET		Primary operation	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age								
18−39 y	Too few events	—	Too few events	—	Too few events	—	Too few events	—
40−49 y	1	Ref	1	Ref	1	Ref	1	Ref
50−59 y	1.00 (0.94−1.07)	0.99	(0.77 0.68−0.87)	< 0.01	(0.84 0.50−01.40)	0.50	(1.00 0.96−1.05)	0.90
60−69 y	1.05 (0.98−1.13)	0.19	(0.67 0.59−0.78)	< 0.01	(0.61 0.35−1.06)	0.08	(0.87 0.83−0.92)	< 0.01
70−79 y	1.14 (1.03−1.25)	0.01	(0.64 0.53−0.78)	< 0.01	(0.81 0.44−1.51)	0.51	(0.84 0.79−0.89)	< 0.01
80 y or older	1.32 (1.15−1.51)	< 0.01	(0.61 0.47−0.78)	< 0.01	(1.56 0.82−2.98)	0.17	(1.22 1.13−1.32)	< 0.01
Race								
White	1	Ref	1	Ref	1	Ref	1	Ref
Black	0.98 (0.91−1.05)	0.49	(1.26 1.10−1.45)	< 0.01	(1.27 0.78−2.10)	0.34	(1.46 1.38−1.53)	< 0.01
Hispanic	1.12 (1.01−1.24)	0.03	(1.08 0.89−1.30)	0.45	(1.19 0.65−2.18)	0.58	(1.19 1.11−1.27)	< 0.01
Asian	1.22 (1.09−1.36)	< 0.01	(1.41 1.15−1.71)	< 0.01	(0.92 0.39−2.18)	0.85	(0.93 0.85−1.01)	0.10
Comorbidity index								
0	1	Ref	1	Ref	1	Ref	1	Ref
1	1.13 (1.05−1.21)	< 0.01	(1.13 0.99−1.29)	0.06	(0.94 0.60−1.45)	0.76	(1.05 1.01−1.10)	00.02
2	1.33 (1.14−1.54)	< 0.01	(1.27 0.97−1.67)	0.08	(1.21 0.62−2.38)	0.58	(1.13 1.03−1.24)	0.01
≥ 3	1.36 (1.05−1.76)	0.02	(1.26 0.73−2.16)	0.40	(1.92 0.85−4.31)	0.11	(1.12 0.95−1.31)	0.18
Insurance								
Private	1	Ref	1	Ref	1	Ref	1	Ref
Medicare	0.93 (0.87−0.99)	0.04	0.93 0.81−1.06)	0.27	(1.54 0.99−2.37)	0.06	(0.98 0.93−1.02)	0.31
Medicaid	1.06 (0.95−1.18)	0.28	1.30 1.08−1.57)	0.01	(1.69 0.97−2.95)	0.06	(1.27 1.19−1.36)	< 0.01
Uninsured	0.90 (0.74−1.09)	0.28	0.84 0.60−1.18)	0.31	(0.55 0.12−2.44)	0.43	(1.28 1.13−1.44)	< 0.01
Facility type								
Community	1	Ref	1	Ref	1	Ref	1	Ref
Comprehensive	1.26 (1.14−1.38)	< 0.01	(1.26 1.05−1.52)	< 0.01	(1.60 0.80−3.20)	0.18	(0.96 0.91−1.02)	0.17
Academic	1.53 (1.38−1.69)	< 0.01	(1.81 1.49−2.19)	< 0.01	(1.81 0.91−3.63)	0.09	(0.96 0.90−1.02)	0.15
Integrated network	1.29 (1.15−1.44)	< 0.01	(1.54 1.25−1.89)	< 0.01	(1.64 0.79−3.44)	0.19	(0.91 0.86−0.97)	0.01
Histology								
Ductal	1	Ref	1	Ref	1	Ref	1	Ref
Lobular	NA	—	NA	—	(1.75 1.21−2.53)	< 0.01	(1.50 1.44−1.57)	< 0.01
Mixed	0.13 (0.12−0.14)	< 0.01	(0.08 0.06−0.10)	< 0.01	(1.25 0.80−1.96)	0.32	(1.13 1.08−1.19)	< 0.01
cT								
cT1	NA all cTis	—	—	—	1	Ref	1	Ref
cT2	—	—	—	—	(0.36 0.26−0.50)	< 0.01	(0.47 0.45−0.49)	< 0.01
Operation type								
BCS	1	Ref	1	Ref	1	Ref	1	Ref
Mastectomy	2.76 (2.63−2.90)	< 0.01	(2.14 1.96−2.35)	< 0.01	(3.07 2.26−4.17)	< 0.01	(2.82 2.73−2.91)	< 0.01
Operation timing								
<60 d	1	Ref	1	Ref	1	Ref	1	Ref
60−120 d	1.15 (1.08−1.22)	< 0.01	(1.09 0.97−1.23)	0.14	(1.01 0.64−1.61)	0.96	(0.92 0.88−0.97)	< 0.01
> 120 d	1.44 (1.24−1.68)	< 0.01	(1.36 1.01−1.82)	0.04	(1.46 0.94−2.29)	0.09	(1.06 0.90−1.25)	0.48

BCS, breast-conserving surgery; cT, clinical tumor category, DCIS, ductal carcinoma in situ; ER, estrogen receptor; NA, not applicable; NET, neoadjuvant endocrine therapy; OR, odds ratio; Ref, reference.

more likely to be upstaged than those undergoing BCS (ER+: OR 2.76; 95% CI, 2.63 to 2.90; ER−: OR 2.14; 95% CI, 1.96 to 2.35).

In total, a larger proportion of T1N0 NET patients (9.7%) were upstaged compared with the T2N0 NET patients (4.8%) (Table 2). The proportion of patients who

Table 4. Cox Proportional Hazards Model Comparing 5-year Overall Survival by Disease Subtype, 2010 to 2015, According to Clinical Disease Stage and Initial Treatment Strategy

	DCIS		NET		Primary operation	
Variable	**ER+**	**ER−**	**cT1N0**	**cT2N0**	**cT1N0**	**cT2N0**
Median follow-up time, mo	41.6	42.4	33.7	36.3	40.1	40.9
Time to operation						
< 60 d	98.1	97.0	94.6	87.8	96.7	92.6
61−120 d	97.9	96.8	97.6	91.8	95.8	91.8
> 120 d	97.4	96.6	96.9	91.5	94.7	90.8
p Value timing	0.085	0.669	0.129	0.538	< 0.001	0.046

Adjusted for age, race, Charlson Comorbidity Index score, insurance, region, grade, histology, operation type, path T/N, adjuvant therapy.
DCIS, ductal carcinoma in situ; ER, estrogen receptor; NET, neoadjuvant endocrine therapy.

were upstaged on final pathology increased by time to operation among the T1N0 NET patients ($p < 0.03$), but not the T2N0 NET patients ($p = 0.455$) (Fig. 2). Of the cT2N0 NET patients, 80% of those with clinical stage IB disease, 62% of those with stage IIA disease, and 65.5% of those with stage IIB disease were downstaged on final pathology. On adjusted analysis, NET patients undergoing operations more than 60 days after diagnosis were not more likely to be upstaged on final pathology compared with those undergoing operations in 60 or fewer days (Table 3). Patients with lobular disease were more likely to be upstaged (OR 1.75; 95% CI, 1.21 to 2.53) compared with those with ductal or mixed histologies. NET patients undergoing mastectomy also had higher odds of upstaging on final pathology (OR 3.07; 95% CI, 2.26 to 4.17), although those who were initially staged as having cT2 disease compared with those with cT1 disease were less likely to be upstaged (OR 0.36; 95% CI, 0.26 to 1.47).

Among primary operation patients, 7.5% of cT1N0 patients and 5.4% of cT2N0 patients were upstaged on final pathology. The proportion of patients who were upstaged increased by time to operation (cT1N0: 7.7% in the fewer than 60 days group compared with 11.1% in the more than 120 days group; cT2N0: 5.4% in the fewer than 60 days group compared with 6.6% in the more than 120 days group) ($p < 0.001$ for both). However, on adjusted analysis, time to operation was not

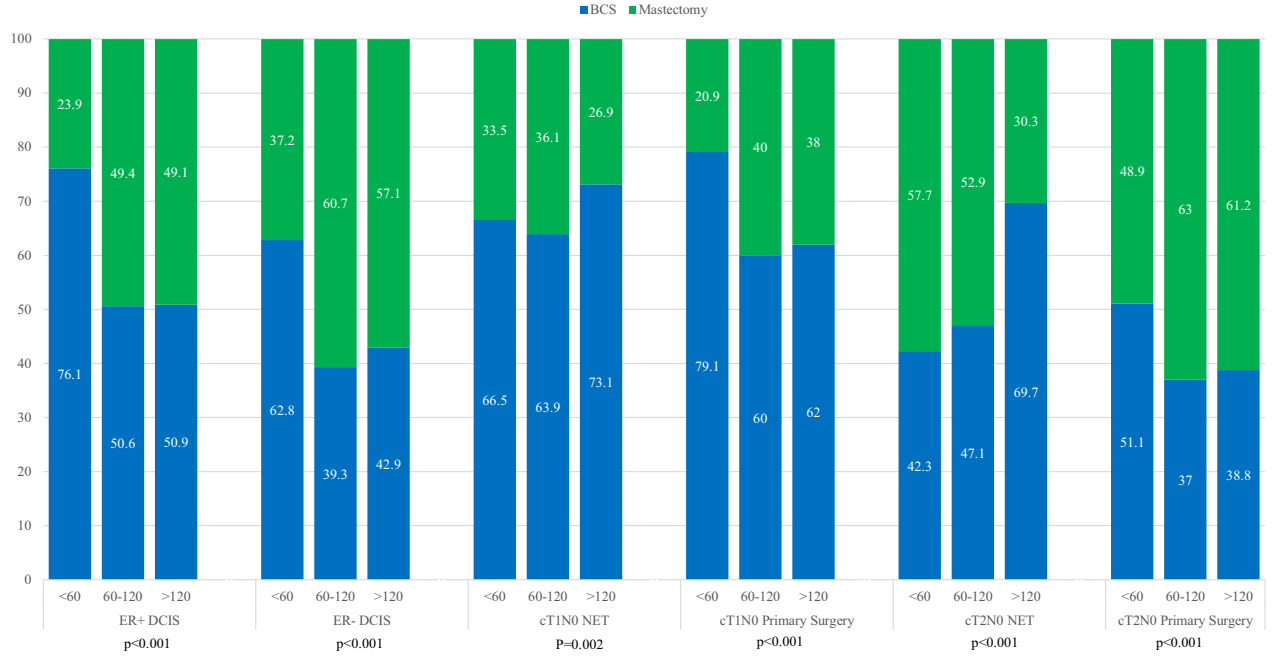

Figure 3. Breast operation type by time to operation, stratified by disease subtype and initial treatment strategy; time to operation in days. BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; ER, estrogen receptor; NET, neoadjuvant endocrine therapy.

significantly associated with pathologic upstaging. Patients with lobular disease and mixed histologies were more likely to be upstaged (lobular: OR 1.50; 95% CI, 1.21 to 2.53; mixed: 1.13, 95% CI, 1.08 to 1.19) compared with those with a ductal histology. Mastectomy patients in this group, as in the DCIS and NET groups, had higher odds of upstaging on final pathology (OR 2.82; 95% CI, 2.73 to 2.91). As in the NET group, those who were initially staged as having cT2 disease compared with those with cT1 disease were less likely to be upstaged (OR 0.47; 95% CI, 0.45 to 0.49).

Association between time to operation and overall survival

Median follow-up time ranged from 33.7 months to 42.4 months by subgroup (Table 4). No significant difference in OS was seen by time to operation among the ER+ ($p = 0.085$) and ER− DCIS patients ($p = 0.669$), cT1N0 NET patients ($p = 0.129$), or cT2N0 NET patients ($p = 0.538$). In the primary operation group, a slight decrease in OS was seen in both the cT1N0 group (OS 96.7% in the fewer than 60 days to operation group vs 94.7% in the more than 120 days to operation group; $p < 0.001$) and the cT2N0 group (OS was 92.6% in the fewer than 60 days to operation group vs 90.8% in the more than 120 days to operation group; $p = 0.046$).

Association between time to operations and breast operation

Among patients with DCIS and among those with cT1-2N0 disease undergoing primary operation, mastectomy rates increased with longer time to operation (eg ER+ DCIS: 23.9% in the fewer than 60 days group vs 49.1% in the more than 120 days group; ER− DCIS: 37.2% in the 60 or fewer days group vs 57.1% in the more than 120 days group; $p < 0.001$ for both). In the NET groups, however, mastectomy rates overall decreased by time, with the clearest trend in the cT2N0 NET group (57.7% in the 60 or fewer days group vs 30.3% in the more than 120 days group; $p < 0.001$) (Fig. 3).

DISCUSSION

Oncologic surgery triage recommendations during the COVID-19 pandemic were based on best available evidence, but admittedly, as unprecedented circumstances forced unconventional practices, some extrapolations from existing data were necessary. Questions remain about the possible effect of the proposed delay strategies on oncologic outcomes. Our study found that on adjusted analyses, surgical delays of more than 120 days were associated with pathologic upstaging in patients with DCIS but not in those with invasive disease. In DCIS patients and cT1-2N0 patients treated with NET, no survival differences were noted by time to operation.

The anxiety of nonoperative management of DCIS stems from known sampling error on core biopsy with pathologic upstaging rates ranging from 10% to 30% at the time of operation.[2,12] Although nonoperative treatment of non-high-grade DCIS is being explored in randomized clinical trials in Europe and the US (eg LORD [Low Risk DCIS],[13] LORIS [Low Risk DCIS],[14] and COMET [Comparison of Operative to Monitoring and Endocrine Therapy for Low-Risk DCIS] trials),[15] these trials are enrolling highly selected patients and have yet to report their results. In addition, retrospective data have shown that in patients meeting LORIS criteria, upstage rates at the time of operation might be 7% to 20%.[16,17] The prospect of leaving patients with undiagnosed and untreated invasive disease can engender discomfort in surgeons and patients alike.

The association between pathologic upstaging and time to operation in DCIS patients has previously been studied in the NCDB, with results consistent with ours, although patients were not stratified by ER status.[2] The possible mitigating effect of NET on disease progression in ER+ DCIS has been demonstrated in a small series,[18] and was part of the recommended delay strategies during the pandemic. Although there were too few DCIS patients on NET to render an adequate analysis in the current study, taken together, these data suggest that initiation of NET in patients with ER+ DCIS is a reasonable delay strategy. For patients with ER− DCIS in whom NET is not a viable option, the consequences of leaving disease in place for longer periods of time remain unclear. Our findings are similar to a previous single-institution study that demonstrated a significantly higher upgrade rate among patients with ER− DCIS,[17] although it is unclear to what extent this phenomenon is driven by grade vs ER status alone.

A previous study has suggested that longer time to operation in DCIS patients can have a small but statistically significant impact on OS.[2] This is likely mediated by the increased rates of invasive disease found on excision, although a previous analysis of Surveillance, Epidemiology, and End Results program data suggests that breast cancer-specific mortality can be observed even in women who never had an invasive cancer diagnosis.[19] The lack of survival difference by time to operation in our analysis might be due to short follow-up time and to the fact that we did not separate the upstaged patients from the patients with pure DCIS on final pathology. Given that the clinical question during the pandemic applied to patients in limbo between their DCIS diagnosis and surgical intervention, our finding that OS does not differ by time to operation

in both ER+ and ER− disease answers a different question than addressed by previous studies.

For patients with early-stage ER+ breast cancer, NET is not currently widely used in the US.[20,21] Similar in-breast tumor response rates have been noted in patients undergoing NET compared with those undergoing neoadjuvant chemotherapy,[5] with 50% to 80% of women seeing partial or complete in-breast responses.[6,22] Although patients with cT1N0 disease were included in studies of primary endocrine therapy alone, which examined the difference in survival between older women undergoing primary endocrine therapy vs operation and endocrine therapy,[8-10] NET has primarily been explored in patients with stage II to III disease in whom the intent was to downstage the primary tumor.[5] As such, the NET population in the NCDB, especially those with clinical T1 disease included in this study, represents a highly selected group. As our multivariable analysis shows, there are specific patient characteristics (ie older age, higher Charlson Comorbidity Index score, and not having private insurance) and disease characteristics (lower grade and having a cT2 tumor compared with a cT1 tumor) that were associated with a higher likelihood of receiving NET. The bias toward older patients with more comorbidities is not surprising, as NET studies have demonstrated the possibility of favorable tumor response with a more favorable toxicity profile than chemotherapy,[5] but does limit the applicability of our findings to the wider population affected by the COVID-19 surgical delays.

The lack of association between time to operation and pathologic upstaging in the NET group in our study is to be expected, given the tumor response rates reported in previous NET studies, and supports the recommendations made by the COVID-19 Pandemic Breast Cancer Consortium. The absence of a survival difference by time to operation is also consistent with the lack of difference in OS found in the primary endocrine therapy trials.[8-10] In addition, most patients with cT2N0 disease were downstaged on final pathology. Although the absolute number of patients is small, there might be some positive, albeit unintended, effects of this particular COVID strategy.

The relationship between time to operation and pathologic upstaging in patients with invasive breast cancer has been mixed. One modeling study in pregnant patients found an association between time to operation and increased risk of positive nodes, with a 3-month delay in operation carrying an associated 2.6% increase in risk of positive lymph nodes. This has not been validated in an actual patient population.[3] In a population of clinically node-negative patients with early-stage breast cancer treated at the MD Anderson Cancer Center, time to operation was not associated with pathologically positive lymph nodes on adjusted analyses.[4]

Survival analyses have similarly reported mixed results, with some reporting a statistically significant association between time to operation and decreased survival,[23-25] and others finding no such association.[26-28] Our analysis found a slight decrease in OS (approximately 2%) at a median follow-up of 40 months in patients who underwent primary operation more than 120 days after diagnosis compared with those who underwent operation within the first 60 days. Although a survival difference might be surprising in early-stage disease, this is consistent with a Surveillance, Epidemiology, and End Results program/NCDB analysis from Bleicher and colleagues,[24] which found that time to operation was associated with lower OS in patients with stage I/II disease, but not with stage III disease. Although we were able to adjust for certain patient, disease, and treatment factors, there are likely unmeasured factors underlying delays in treatment in this population, which might be responsible for the slight decrement in OS. For example, previous studies have noted that cohorts who undergo operation farther out from the time of diagnosis have higher proportions of Medicaid, uninsured, black, Hispanic, and lower-income patients.[25] In addition, among a cohort of Medicaid patients in North Carolina, differences in survival by time to treatment were noted not among early-stage patients, but among late-stage patients.[23] The relationship between survival and time to treatment might be significantly modified by socioeconomic and disease factors. Yet as increased time to operation during the COVID-19 pandemic was driven by different factors, the small OS difference might not hold true when outcomes of these patients are analyzed in the future.

Unmeasured factors likely also underlie the association between time to operation and the extent of breast operation. The increase in mastectomy rates by time to operation in the DCIS and primary operation groups might not be linked to extent of disease; rather it might be a factor as simple as surgical scheduling that accounts for the greater proportions of mastectomies among patients undergoing operations more than 60 days after diagnosis. Reconstruction, although not explored in our current analysis, has previously been associated with longer time to operation.[4,24] Extent of breast operations in early-stage disease is also subject to patient preference, with a variety of non-disease-related factors driving a patient's decision to undergo mastectomy.[29-31]

Our study has several limitations. First, as mentioned previously, the applicability of our findings is limited, given that that populations experiencing delays in surgical therapy and who were selected for NET in this

retrospective analysis are more select then the patients who have experienced surgical delays during the pandemic. We would assert, however, that these are the best data currently available to study the possible outcomes of oncologic surgical delays. Second, to take advantage of the most current variables in the NCDB (eg HER2 status), and given that NET use in the US has only recently begun to be more widely adopted, our analysis was limited to 2010 through 2016, rendering our follow-up time relatively short. Third, using the American Joint Committee on Cancer 8th edition prognostic staging allowed us to more accurately judge rates of meaningful (ie prognostic) differences in upstaging, but the pathologic staging system does require more known data points (ie tumor grade, nodal status, HR-status, and HER-2 status). As such, not all of the patients with invasive cancer could be definitively staged pathologically. Finally, adherence to endocrine therapy cannot be assessed in the NCDB; this is a significant issue in breast cancer patients on endocrine therapy, which can influence OS.[32] Due to the retrospective nature of the NCDB, however, our reported survival data likely capture a "real-world" population of adherers and nonadherers alike.

CONCLUSIONS

In this analysis, surgical delays of more than 60 days were associated with pathologic upstaging in patients with DCIS but not in those with invasive disease. No survival differences in patients with DCIS or early-stage ER+ breast cancer on NET were noted by time to operation. Although the applicability of these data to the patients experiencing surgical delays during the COVID-19 pandemic is limited, surgeons and patients might find some reassurance in these findings, as these 2 groups represent patients significantly affected by the surgical triage recommendations of the COVID-19 Pandemic Breast Cancer Consortium. Future study of outcomes of patients treated during this time will be required to determine the actual impact of COVID-related surgical delays and delay strategies.

Author Contributions

Study conception and design: Minami, Kantor, King, Mittendorf

Acquisition of data: Kantor, Weiss

Analysis and interpretation of data: Minami, Kantor, Weiss, King, Mittendorf

Drafting of manuscript: Minami, Kantor

Critical revision: Minami, Kantor, Weiss, Nakhlis, King, Mittendorf

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eTable 1. Univariable Analysis of Factors Associated with Upgrade by the American Joint Committee on Cancer 8th Edition Prognostic Staging

	ER+ DCIS		ER− DCIS		NET		Primary operation	
Patient characteristic	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Age								
18−39 y	1	Ref	1	Ref	1	Ref	1	Ref
40−49 y	0.44 (0.40−0.49)	< 0.01	0.67 (0.55−0.82)	< 0.01	0.55 (0.22−1.33)	0.18	0.57 (0.53−0.61)	< 0.01
50−59 y	0.38 (0.34−0.42)	< 0.01	0.45 (0.37−0.55)	< 0.01	0.39 (0.17−0.92)	0.03	0.50 (0.47−0.54)	< 0.01
60−69 y	0.36 (0.32−0.40)	< 0.01	0.35 (0.28−0.42)	< 0.01	0.28 (0.12−0.66)	0.01	0.40 (0.38−0.44)	< 0.01
70−79 y	0.37 (0.33−0.41)	< 0.01	0.32 (0.26−0.40)	< 0.01	0.42 (0.18−0.99)	0.05	0.38 (0.35−0.41)	< 0.01
80+ y	0.42 (0.36−0.48)	< 0.01	0.30 (0.23−0.39)	< 0.01	0.74 (0.21−1.77)	0.50	0.56 (0.51−0.61)	< 0.01
Race								
White	1	Ref	1	Ref	1	Ref	1	Ref
Black	1.05 (0.98−1.12)	0.16	1.31 (1.15−1.49)	< 0.01	1.46 (0.93−2.28)	0.10	1.48 (1.41−1.55)	< 0.01
Hispanic	1.14 (1.05−1.25)	< 0.01	1.33 (1.13−1.57)	< 0.01	0.97 (0.55−1.71)	0.93	1.28 (1.20−1.36)	< 0.01
Asian	1.24 (1.12−1.37)	< 0.01	1.45 (1.21−1.73)	< 0.01	0.95 (0.43−2.07)	0.90	1.01 (0.93−1.09)	0.87
Charlson Comorbidity Index								
0	1	Ref	1	Ref	1	Ref	1	Ref
1	1.10 (1.03−1.17)	0.01	1.08 (0.96−1.22)	0.20	0.99 (0.65−1.51)	0.98	1.04 (1.00−1.09)	0.05
2	1.22 (1.06−1.41)	0.01	1.14 (0.89−1.47)	0.31	1.39 (0.74−2.64)	0.31	1.09 (0.99−1.20)	0.05
≥ 3	1.32 (1.03−1.69)	0.03	0.95 (0.57−1.57)	0.83	2.19 (1.02−4.70)	0.04	1.09 (0.93−1.27)	0.30
Insurance								
Private	1	Ref	1	Ref	1	Ref	1	Ref
Medicare	0.89 (0.84−0.93)	< 0.01	0.69 (0.63−0.76)	< 0.01	1.36 (1.00−1.84)	0.05	0.84 (0.82−0.87)	< 0.01
Medicaid	1.18 (1.07−1.30)	< 0.01	1.48 (1.25−1.75)	< 0.01	1.77 (1.07−2.94)	0.03	1.32 (1.24−1.40)	< 0.01
Uninsured	1.13 (0.95−1.35)	0.17	1.06 (0.78−1.44)	0.72	0.53 (0.13−2.21)	0.39	1.32 (1.18−1.48)	< 0.01
Facility type								
Community	1	Ref	1	Ref	1	Ref	1	Ref
Comprehensive	1.26 (1.14−1.39)	< 0.01	1.24 (1.04−1.49)	0.02	1.54 (0.78−3.01)	0.21	0.99 (0.93−1.04)	0.65
Academic	1.40 (1.27−1.54)	< 0.01	1.69 (1.41−2.04)	< 0.01	1.68 (0.85−3.29)	0.13	1.02 (0.96−1.08)	0.56
Integrated network	1.25 (1.12−1.39)	< 0.01	1.48 (1.21−1.80)	< 0.01	1.52 (0.74−3.12)	0.26	0.96 (0.90−1.02)	0.17
Histology								
Ductal	1	Ref	1	Ref	1	Ref	1	Ref
Lobular	NA	—	NA	—	1.66 (1.18−2.35)	< 0.01	1.54 (1.48−1.61)	< 0.01
Mixed	0.14 (0.13−1.15)	< 0.01	0.08 (0.07−0.10)	< 0.01	1.23 (0.81−1.88)	0.37	1.17 (1.11−1.22)	< 0.01
cT								
cT1	NA (all cTis)	Ref	NA (all cTis)	—	1	Ref	1	Ref
cT2	—	—	—	—	0.47 (0.35−0.63)	< 0.01	0.67 (0.64−0.70)	< 0.01
Operation type								
BCS	1	Ref	1	Ref	1	Ref	1	Ref
Mastectomy	2.82 (2.70−2.95)	< 0.01	2.36 (2.17−2.56)	< 0.01	2.80 (2.11−3.72)	< 0.01	2.60 (2.53−2.68)	< 0.01
Operation timing								
< 60 d	1	Ref	1	Ref	1	Ref	1	Ref
60−120 d	1.43 (1.35−1.52)	< 0.01	1.32 (1.19−1.47)	< 0.01	0.97 (0.63−1.51)	0.90	1.21 (1.16−1.27)	< 0.01
> 120 d	1.75 (1.52−2.01)	< 0.01	1.70 (1.30−2.21)	< 0.01	1.01 (0.67−1.51)	0.98	1.42 (1.21−1.66)	< 0.01

BCS, breast-conserving surgery; cT, clinical tumor category, DCIS, ductal carcinoma in situ; ER, estrogen receptor; NET, neoadjuvant endocrine therapy; OR, odds ratio; Ref, reference.

eTable 2. Multivariable Analysis of Factors Associated with Neoadjuvant Endocrine Therapy Receipt

Patient characteristic	OR (95% CI)	p Value
Age		
18–39 y	1	Ref
40–49 y	1.02 (0.73–1.41)	0.93
50–59 y	1.41 (1.02–1.93)	0.04
60–69 y	1.73 (1.26–2.38)	< 0.01
70–79 y	1.92 (1.38–2.66)	< 0.01
80+ y	2.63 (1.88–3.69)	< 0.01
Race		
White	1	Ref
Black	1.06 (0.93–1.21)	0.38
Hispanic	1.35 (1.17–1.56)	< 0.01
Asian	1.07 (0.88–1.30)	0.50
Charlson Comorbidity Index		
0	1	Ref
1	0.88 (0.79–0.97)	0.01
2	1.32 (1.10–1.59)	< 0.01
≥ 3	1.83 (1.41–2.39)	< 0.01
Insurance		
Private	1	Ref
Medicare	1.16 (1.05–1.29)	< 0.01
Medicaid	1.47 (1.26–1.70)	< 0.01
Uninsured	1.53 (1.18–1.99)	< 0.01
Region		
Metro	1	Ref
Urban	1.02 (0.91–1.13)	0.77
Rural	1.06 (0.81–1.39)	0.66
Unknown	1.17 (0.95–1.45)	0.15
Facility type		
Community	1	Ref
Comprehensive	1.13 (0.97–1.30)	0.11
Academic	1.62 (1.40–1.87)	< 0.01
Integrated Network	1.59 (1.36–1.87)	< 0.01
Histology		
Ductal	1	Ref
Lobular	1.17 (1.06–1.29)	< 0.01
Mixed	1.09 (0.98–1.22)	0.12
Grade		
1	1	Ref
2	0.80 (0.74–0.87)	< 0.01
3	0.45 (0.40–0.51)	< 0.01
cT		
cT1	1	Ref
cT2	5.40 (5.01–5.81)	<0.01

cT, clinical tumor category; OR, odds ratio; Ref, reference.