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Time to Surgery and Breast Cancer Survival in the United States

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IMPORTANCE Time to surgery (TTS) is of concern to patients and clinicians, but controversy surrounds its effect on breast cancer survival. There remains little national data evaluating the association.

OBJECTIVE To investigate the relationship between the time from diagnosis to breast cancer surgery and survival, using separate analyses of 2 of the largest cancer databases in the United States.

DESIGN, SETTING, AND PARTICIPANTS Two independent population-based studies were conducted of prospectively collected national data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare–linked database and the National Cancer Database (NCDB). The SEER-Medicare cohort included Medicare patients older than 65 years, and the NCDB cohort included patients cared for at Commission on Cancer–accredited facilities throughout the United States. Each analysis assessed overall survival as a function of time between diagnosis and surgery by evaluating 5 intervals (≤30, 31-60, 61-90, 91-120, and 121-180 days) and disease-specific survival at 60-day intervals. All patients were diagnosed with noninflammatory, nonmetastatic, invasive breast cancer and underwent surgery as initial treatment.

MAIN OUTCOMES AND MEASURES Overall and disease-specific survival as a function of time between diagnosis and surgery, after adjusting for patient, demographic, and tumor-related factors.

RESULTS The SEER-Medicare cohort had 94 544 patients 66 years or older diagnosed between 1992 and 2009. With each interval of delay increase, overall survival was lower overall (hazard ratio [HR], 1.09; 95% CI, 1.06-1.13; $P < .001$), and in patients with stage I (HR, 1.13; 95% CI, 1.08-1.18; $P < .001$) and stage II disease (HR 1.06; 95% CI, 1.01-1.11; $P = .01$). Breast cancer–specific mortality increased with each 60-day interval (subdistribution hazard ratio [sHR], 1.26; 95% CI, 1.02-1.54; $P = .03$). The NCDB study evaluated 115 790 patients 18 years or older diagnosed between 2003 and 2005. The overall mortality HR was 1.10 (95% CI, 1.07-1.13; $P < .001$) for each increasing interval, significant in stages I (HR, 1.16; 95% CI, 1.12-1.21; $P < .001$) and II (HR, 1.09; 95% CI, 1.05-1.13; $P < .001$) only, after adjusting for demographic, tumor, and treatment factors.

CONCLUSIONS AND RELEVANCE Greater TTS is associated with lower overall and disease-specific survival, and a shortened delay is associated with benefits comparable to some standard therapies. Although time is required for preoperative evaluation and consideration of options such as reconstruction, efforts to reduce TTS should be pursued when possible to enhance survival.

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Delays in the treatment of breast cancer have been feared for decades, as even William Halsted proclaimed in 1907 that "we no longer need the proof…[that] the slightest delay is dangerous…in the early stage of breast cancer."[1] There is little doubt that waiting for treatment causes anxiety, but the published medical literature has not provided a consistent answer as to whether any specific preoperative time to surgery (TTS) is associated with an effect on overall or disease-specific survival.

There has been a movement to include TTS as a breast cancer quality measure,[2-4] but only recently has this preoperative interval and the relationship of patient evaluation components to delay been comprehensively evaluated in Medicare patients.[5] We have found that while the interval between presentation and surgery in Medicare patients is short, that time interval has been rising, from 21 days in 1992 to 32 days in 2005.[5]

This report details 2 separate studies undertaken to evaluate the relationship between TTS and survival using 2 of the largest data sets in existence for the United States population: the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database and the National Cancer Database (NCDB). If breast cancer survival is a function of the time between diagnosis and surgery, efforts to expedite care may be of value because of the outcome benefit that occurs.

At a Glance

- This study was performed to determine if time from diagnosis to surgery correlated with overall survival (OS) and disease-specific survival (DSS) in 2 large national data sets.
- Longer time from diagnosis to breast cancer surgery was associated with a decline in OS and DSS, when adjusting for patient, tumor, and treatment factors.
- Overall survival declined for each interval increase in the Surveillance, Epidemiology, and End Results (SEER)-Medicare cohort (hazard ratio [HR], 1.09; $P < .001$) and the National Cancer Database cohort (HR, 1.10; $P < .001$), with the decline most pronounced in stages I and II disease.
- Disease-specific survival declined for each interval increase in the SEER-Medicare cohort (HR 1.26, $P = .03$), with the decline most pronounced in stage I disease.
- Efforts should be made to reduce the time to surgery when possible to enhance overall and breast cancer–specific survival.

Methods

The SEER-Medicare and NCDB analyses were each approved by, and the need for informed consent waived by, the Fox Chase Cancer Center institutional review board. Permission to use the SEER-Medicare and NCDB datasets were obtained, respectively, from the National Cancer Institute (NCI) and American College of Surgeons. The data and analyses were kept separate, and no attempts were made to compare data between cohorts nor to determine whether patients overlapped, for privacy reasons and to comply with NCI requirements. Both analyses are presented here because of the representativeness of each cohort and the consistent findings. No statistical analysis between the cohorts has been attempted, nor is one warranted because the populations, variable definitions, and ranges differ.

Time intervals between diagnosis and surgery were set at 30-day increments, with the last 2 intervals combined owing to smaller numbers in each. Intervals to assess overall survival (OS) were thus categorized as 30 days or less, 31 to 60 days, 61 to 90 days, 91 to 120 days, and 121 to 180 days, while disease-specific survival (DSS) intervals were characterized as 60 days or less, 61 to 120 days, and 121 to 180 days because of the lower rate of cancer-specific events and to minimize estimator variance. Time from diagnosis was used for OS and DSS so that patients would have a uniform starting time.

Race/ethnicity was included in the analysis to make the results more generalizable to the US population. Propensity score–based weighting, to adjust for confounding, was used to adjust for covariate differences in the time-interval groups.[6] We used multinomial logistic regression to estimate the propensity scores, stabilized them to improve covariate balance,[7] and used restricted cubic splines for continuous covariates.[8] We created adjusted OS curves and adjusted cause-specific cumulative incidence functions using the inverse probability weight method.[9] Cox proportional hazards regression with propensity score–based weights were used to estimate the hazard ratios (HRs) associated with the time interval groupings and OS. Fine and Gray[10] proportional hazards regression with propensity score–based weights was used to estimate the subdistribution hazard ratios (sHRs) associated with the interval length and breast cancer–specific mortality. We used bootstrap standard errors for hypothesis testing and 95% confidence intervals; the bootstrap method accounted for propensity score estimation. Differences in the effect of preoperative time interval by American Joint Committee on Cancer (AJCC) stage were examined via propensity score–based weighted regressions in which we included main effect terms for stage (2 dummy indicators), the preoperative time interval variable (ordinal variable), and interactions of AJCC stage indicators with that interval length.

SEER-Medicare Database

SEER-Medicare patients were diagnosed between 1992 and 2009 with invasive, noninflammatory, nonmetastatic breast cancer. They had surgery as first therapy and a definitive surgery date in Medicare claims of 180 days or less after diagnosis. Exclusions included those having missing covariate data and those younger than 66 years to permit comorbidity assessment 12 months prior to diagnosis. Although patients were restricted to their first breast cancer occurrence, a history of other malignant neoplasms was permitted. While substage (ie, IIA, IIB) migration between AJCC editions can occur in nearly 20% of patients, stage migration occurs in less than 0.2%,[11] so substages were collapsed and not differentiated by edition. The diagnosis date, used as the preoperative interval start date, was determined by using SEER clinical diagnosis date (which only consists of a month and year) and searching for the first biopsy date during that month or the subsequent month. Patients were excluded who had no such discernable biopsy date.

Because procedure codes for excisional biopsy and segmental mastectomy are sometimes used interchangeably in billing, inference of therapeutic intent was achieved by defining a patient's definitive surgery as the first date on which claims for both 1 or more breast excisions or mastectomy and a lymph node procedure were performed (eTable 1 in the Supplement).

Adjustments were made for age, sex, race, marital status, income, education, size of metropolitan area, geographical region, year of diagnosis, sequence of breast cancer (within a history of other cancers), Charlson[12] and Elixhauser[13] comorbidity scores, histologic findings, grade, tumor size, number of lymph nodes examined, number of positive lymph nodes, AJCC stage, surgery type, chemotherapy use, and radiotherapy use, via propensity score–based weighting. Patients receiving neoadjuvant chemotherapy were excluded, and chemotherapy and radiotherapy use were defined as being administered if given 1 year or less after surgery. Race was determined from the Medicare enrollment database variable, while comorbidity, surgery, chemotherapy, and radiotherapy came from Medicare claims. Missing covariate data are listed in eTable 2 in the Supplement.

National Cancer Database

The NCDB[14] cohort included patients having noninflammatory, invasive, nonmetastatic breast cancer. They had surgical treatment as their first treatment 6 months or less after their diagnosis date. Patients were included if breast cancer was their first and only malignant neoplasm and if diagnosis and treatment (all or part) was at the reporting facility. Patients without lymph node surgery or whose staging, diagnosis method, or treatment order was unknown were excluded. The NCDB does not provide a diagnosis date but after 2002 recorded the length of the interval between diagnosis and surgery. This interval length was present for cases diagnosed from 2003 onward. The NCDB requires follow-up of greater than 5 years, so the cohort only included cases from 2003 to 2005 with follow-up through 2010.

The NCDB contains the most extensive surgery (eg, a lumpectomy followed by mastectomy lists the patient as having a mastectomy). The NCDB also contains interval lengths from diagnosis to first surgery and from diagnosis to definitive surgery, to determine if the patient underwent more than 1 procedure. We excluded patients with more than 1 breast procedure to ensure capture of therapeutic surgery and to eliminate possible confounding excisional biopsies, ensuring that the analysis evaluated the time to therapeutic surgery. Patients receiving neoadjuvant chemotherapy were excluded, and chemotherapy and radiotherapy use were defined as being administered if given 1 year or less after surgery. Missing covariate data are listed in eTable 2 in the Supplement.

Adjustments were made for age, sex, race, income, education, size of metropolitan area, geographical region, year of diagnosis, Charlson-Deyo comorbidity score, histologic findings, grade, tumor size, surgical margins, number of nodes examined, number of positive nodes, AJCC stage, surgery type, chemotherapy, radiotherapy, endocrine therapy, facility type, distance to facility, class of case, and insurance type, via propensity score–based weighting.

Results

SEER-Medicare Database

There were 94 544 SEER-Medicare patients analyzed, after all exclusions (eFigure 1 in the Supplement). Mean (SD) age was 75.2 (6.2) years, and 99% were women. Individuals having 30 days or less, 31 to 60 days, 61 to 90 days, 91 to 120 days, and 121 to 180 days between diagnosis and surgery made up 77.7%, 18.3%, 2.7%, 0.7%, and 0.5% of the total number of patients, respectively; patient and tumor characteristics of these groups are listed in **Table 1**, demonstrating greater similarity among the groups after adjustment. Black race and Hispanic ethnicity, lobular histologic findings, fewer nodes examined, large metropolitan region, higher Charlson and Elixhauser comorbidity scores, tumor size, the proportion of stage III tumors, the percentage of patients undergoing mastectomy, and a lack of chemotherapy use increased steadily in the unadjusted data with an increase in the delay interval (Table 1).

The increase in mortality in all stages for all patients and from all causes was 9% (HR, 1.09; 95% CI, 1.06-1.13; $P < .001$) for each preoperative interval category increase (**Figure 1**A). The TTS was statistically significant with respect to OS in stage I (HR, 1.13; 95% CI, 1.08-1.18; $P < .001$) and stage II disease (HR, 1.06; 95% CI, 1.01-1.11; $P = .01$), but not in stage III (HR, 1.06; 95% CI, 0.97-1.16; $P = .17$) (eFigure 2 in the Supplement). The P values for HR interaction for stage I vs stage II was $P = .048$; stage I vs III, $P = 0.21$; and stage II vs III, $P = .95$.

Added risk of death due to breast cancer for each 60-day increase in TTS had a subdistribution hazard ratio [sHR] of 1.26 (95% CI, 1.02-1.54; $P = .03$) (**Figure 2**). The association with disease-specific mortality was significant for stage I disease (sHR, 1.84; 95% CI, 1.10-3.07; $P = .02$) but not for stage II or stage III. The P values for sHR interaction were $P = .04$ for stage I vs II and $P = .06$ for stage I vs III. Adjusted 5-year OS is listed in **Table 2**, and 62.6% of patients were diagnosed before 2005, allowing for at least 5 years of mortality follow-up. The HRs and sHRs from the Cox and Fine and Gray models are listed in eTable 3 in the Supplement. Cardiac and cerebrovascular disease, along with chronic obstructive pulmonary disease were the most frequent nononcologic specified causes of death (eTable 4 in the Supplement).

National Cancer Database

There were 115 790 NCDB patients analyzed, after all exclusions (eFigure 1 in the Supplement). The NCDB patient characteristics are summarized with adjusted and unadjusted data by preoperative interval group in **Table 3** and eTable 5 in the Supplement, demonstrating greater similarity among the groups after adjustment. Mean (SD) patient age was 60.3 (13.4) years, and ages ranged from 18 to 90 years; nearly all were women. Patients who had intervals of 30 days or less, 31 to 60 days, 61 to 90 days, 91 to 120 days, and 121 to 180 days accounted for 69.5%, 24.9%, 4.1%, 1.0%, and 0.5% of the total number of patients, respectively. Unadjusted prevalence of Black and Asian race, higher Charlson comorbidity score, large metropolitan setting, Pacific region of the United

Table 1. Adjusted/Weighted and Unadjusted/Unweighted Patient and Tumor Characteristics From the SEER-Medicare Database Study by Surgery Delay Interval[a]

	Time to Surgery Interval, d				
Characteristic	≤30	31-60	61-90	91-120	121-180
Total patients, No.	73 491	17 345	2586	686	436
Mean age, y	75.2 (75.1)	75.2 (75.3)	75.1 (75.7)	75.5 (75.9)	75.3 (77.2)
Sex					
Female	99.2 (99.1)	99.1 (99.3)	NR[b]	NR[b]	NR[b]
Male	1.0 (0.9)	1.0 (0.7)	NR[b]	NR[b]	NR[b]
Race/ethnicity					
White	89.3 (90.2)	89.1 (86.9)	89.1 (83.3)	88.3 (77.1)	87.9 (75.9)
Black	6.3 (5.5)	6.5 (8.2)	6.8 (11.3)	5.9 (16.3)	7.6 (18.1)
Asian	1.9 (1.8)	1.8 (2.0)	1.8 (2.3)	2.3 (2.0)	1.2 (2.3)
Hispanic	1.0 (0.9)	1.0 (1.2)	1.0 (1.7)	1.3 (1.9)	0.9 (2.3)
Other/unknown	1.6 (1.5)	1.6 (1.7)	1.2 (1.4)	2.6 (1.8)	1.4 (2.1)
Charlson Comorbidity Index, mean	0.5 (0.5)	0.5 (0.6)	0.5 (0.7)	0.5 (0.8)	0.5 (0.8)
Setting[c]					
Large metropolitan	54.6 (51.5)	54.5 (64.6)	53.2 (67.1)	50.4 (67.5)	56.1 (69.0)
Metropolitan	29.1 (30.5)	28.7 (24.3)	28.6 (22.9)	33.2 (21.8)	26.5 (23.2)
Urban	6.0 (6.6)	6.3 (4.4)	7.1 (4.3)	6.2 (3.8)	3.7 (2.3)
Less urban/rural	10.3 (11.4)	10.5 (6.7)	11.1 (5.8)	10.3 (7.0)	13.8 (5.5)
Region[d]					
Northeast	17.4 (16.0)	17.7 (22.2)	17.3 (22.2)	18.0 (23.3)	18.9 (22.9)
South	20.8 (22.4)	20.4 (15.2)	21.0 (13.5)	19.2 (13.6)	18.4 (18.4)
Midwest	18.5 (19.3)	19.0 (15.8)	19.1 (14.2)	19.5 (14.6)	14.9 (12.4)
West	43.3 (42.3)	42.9 (46.8)	42.6 (50.1)	43.3 (48.5)	47.9 (46.3)
Invasive histologic findings					
Ductal	86.6 (86.9)	86.4 (85.9)	86.1 (85.6)	85.8 (85.6)	87.1 (82.3)
Lobular	10.9 (10.6)	11.0 (11.9)	10.7 (11.9)	11.5 (12.0)	11.6 (14.5)
Other/unknown	2.5 (2.6)	2.6 (2.3)	3.3 (2.5)	2.7 (2.5)	1.3 (3.2)
Grade					
Well differentiated	22.2 (21.8)	22.5 (24.1)	22.2 (23.0)	21.3 (20.4)	17.3 (20.2)
Moderately differentiated	41.8 (41.3)	42.1 (43.2)	40.4 (43.2)	43.6 (43.6)	44.5 (42.4)
Poorly differentiated	25.2 (25.6)	24.6 (23.7)	26.0 (24.3)	26.0 (24.8)	28.7 (24.5)
Undifferentiated/ anaplastic	1.3 (1.4)	1.2 (1.0)	1.3 (1.0)	1.0 (1.8)	1.6 (2.3)
Unknown	9.5 (9.9)	9.7 (8.0)	10.2 (8.6)	8.1 (9.5)	7.9 (10.6)
Mean tumor size, mm	19.1 (19.2)	18.9 (18.3)	19.5 (20.1)	20.0 (21.6)	20.4 (26.3)
AJCC stage[e]					
I	57.9 (57.8)	58.4 (59.3)	56.8 (55.2)	50.9 (55.3)	56.2 (44.0)
II	35.9 (36.2)	35.6 (34.5)	37.2 (36.2)	42.6 (33.8)	37.4 (39.5)
III	6.2 (6.0)	6.1 (6.2)	6.0 (8.6)	6.4 (10.9)	6.5 (16.5)
Median income for census tract, $US	50 363 (49 728)	50 312 (52 882)	49 735 (51 649)	49 990 (26 805)	49 549 (21 076)
Education <12 years (high school) by census tract, %[f]	17.6 (17.6)	17.6 (17.2)	18.0 (18.4)	17.5 (20.4)	18.5 (19.5)
Mean year of diagnosis	2002.3 (2001.8)	2002.3 (2004.0)	2002.4 (2004.5)	2002.3 (2004.2)	2002.2 (2004.3)
Marital status					
Married	45.5 (46.7)	45.0 (42.9)	46.6 (36.9)	46.7 (33.5)	41.6 (31.0)
Not married	54.5 (53.3)	55.0 (57.1)	53.4 (63.1)	53.3 (66.5)	58.4 (69.0)
Mean breast cancer sequence[g]	1.1 (1.1)	1.1 (1.1)	1.1 (1.1)	1.1 (1.1)	1.1 (1.1)
Mean Elixhauser score	1.1 (1.0)	1.1 (1.1)	1.1 (1.5)	1.5 (1.7)	1.0 (1.6)
Positive nodes, mean No.	1.0 (1.0)	1.0 (0.9)	0.9 (1.1)	1.0 (1.2)	1.1 (1.5)
Nodes examined, mean No.	8.9 (9.3)	8.8 (7.6)	8.7 (7.3)	8.7 (7.3)	8.0 (7.1)

(continued)

Table 1. Adjusted/Weighted and Unadjusted/Unweighted Patient and Tumor Characteristics From the SEER-Medicare Database Study by Surgery Delay Interval[a] (continued)

Characteristic	Time to Surgery Interval, d				
	≤30	31-60	61-90	91-120	121-180
Surgery type					
Breast conservation	72.7 (73.6)	73.3 (69.9)	73.2 (68.7)	74.6 (64.4)	72.2 (63.5)
Mastectomy	27.3 (26.4)	26.7 (30.1)	26.8 (31.3)	25.4 (35.6)	27.8 (36.5)
Chemotherapy use					
Yes	22.5 (23.0)	21.9 (21.6)	24.7 (18.2)	21.1 (18.5)	26.5 (15.6)
No	77.5 (77.0)	78.0 (78.4)	75.3 (81.8)	78.9 (81.5)	73.5 (84.4)
Radiotherapy use					
Yes	50.9 (50.9)	51.0 (52.7)	51.8 (44.8)	55.4 (38.5)	49.0 (41.7)
No	49.1 (49.1)	49.0 (47.3)	46.2 (55.2)	44.6 (61.5)	51.0 (58.3)

Abbreviations: AJCC, American Joint Committee on Cancer; NR, not reported; SEER, Surveillance, Epidemiology, and End Results.

[a] Unless otherwise indicated, data are reported as adjusted (unadjusted) percentages of patients; totals may vary from 100% due to rounding.

[b] Cells have been deleted per SEER-Medicare requirements to censor cells containing fewer than 11 individuals or other cells that make such cells calculable.

[c] Setting definitions: Large metropolitan indicates counties of metropolitan areas of 1 million population or more; metropolitan, counties in metropolitan areas up to 1 million population; urban, urban population of 20 000 or more adjacent or nonadjacent to a metropolitan area; less urban, urban population of 2500-19 999 adjacentadjacent or nonadjacent to a metropolitan area; rural, completely rural or less than 2500 urban population adjacent or nonadjacent to a metropolitan area.

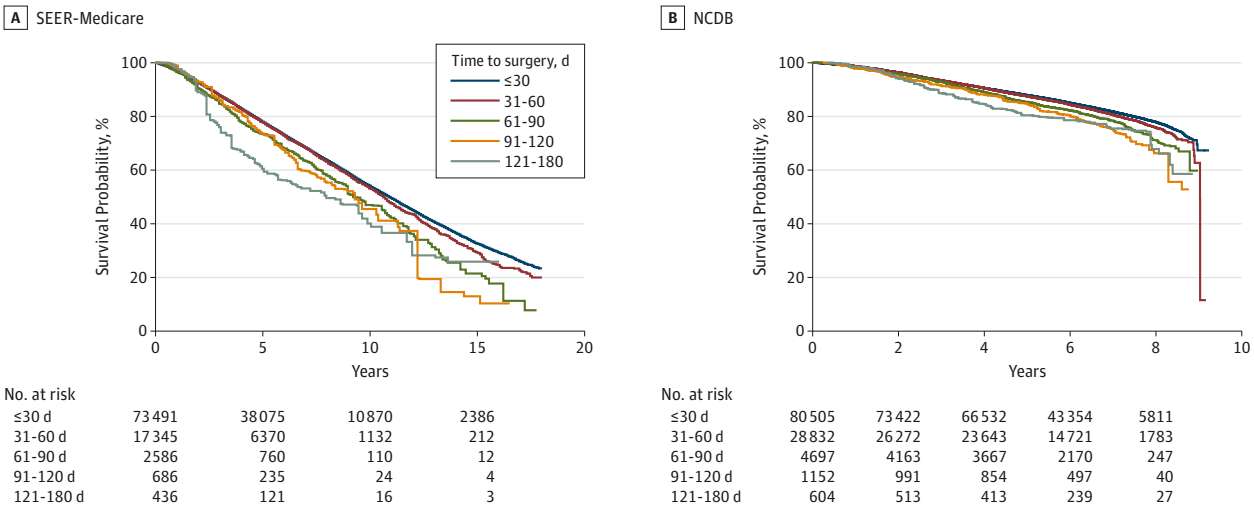
[d] Region groupings: Northeast, Connecticut and New Jersey registries; South, Atlanta, Kentucky, and Louisiana registries; Midwest, Detroit and Iowa registries; West, Hawaii, New Mexico, Seattle, Utah, and California registries. Registries were adjusted individually but are grouped for reporting purposes.

[e] In determining AJCC stage the third and sixth AJCC editions were combined; substages (eg, IIA, IIB) were collapsed to minimize differences between editions.

[f] Percentage of persons 25 years or older.

[g] The number of the cancer, when a patient has 1 or more distinct primary cancers during their lifetime.

Figure 1. Adjusted Overall Survival

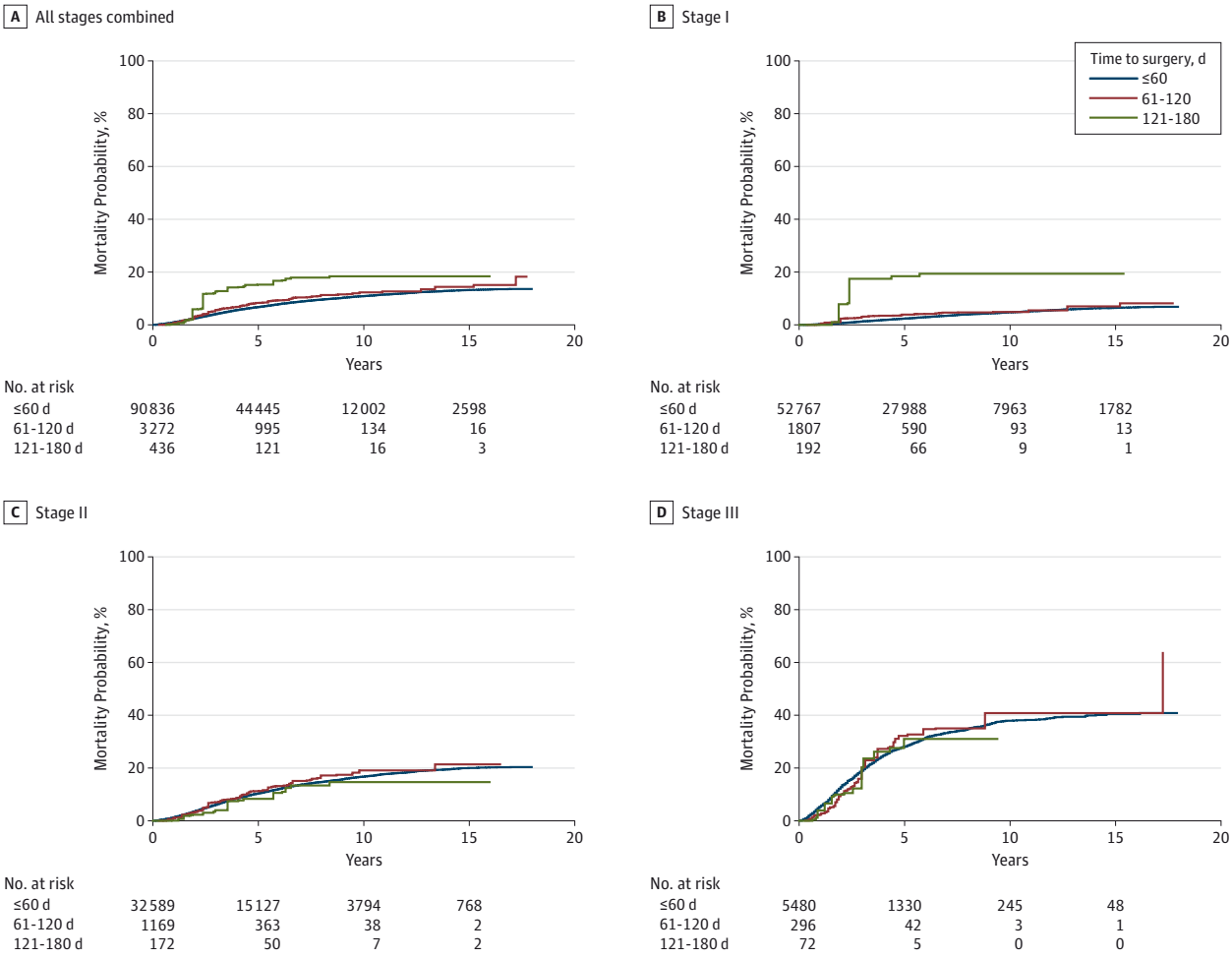


Adjusted overall survival for Surveillance, Epidemiology, and End Results (SEER)-Medicare Database patients (A) and National Cancer Database (NCDB) patients (B) for preoperative delay intervals of ≤30, 31-60, 61-90, 91-120, and 121-180 days. The hazard ratio for each increasing delay in SEER-Medicare interval was 1.09 (95% CI, 1.06-1.13; $P < .001$). The hazard ratio for each increasing delay interval in NCDB was 1.10 (95% CI, 1.07-1.13; $P < .001$).

States, unknown grade/differentiation, stage III tumors, income less than $30 000, zip codes with the highest level of education, the proportion of patients undergoing mastectomy, lack of chemotherapy, radiotherapy, and endocrine therapy use, and a lower proportion of private insurance increased steadily in the unadjusted data with an increase in the delay interval (Table 3).

The added risk of death from all causes for each interval increase in TTS was 10.0% (HR, 1.10; 95% CI, 1.07-1.13; $P < .001$) (Figure 1B) for the entire cohort. The TTS was associated with OS for stage I (HR, 1.16; 95% CI, 1.12-1.21; $P < .001$) and stage II disease (HR, 1.09; 95% CI, 1.05-1.13; $P < .001$) but not stage III (HR, 1.01; 95% CI, 0.96-1.07; $P = .64$) (eFigure 3 in the Supplement). The P values for sHR interaction were $P = .03$ for stage I

Figure 2. Adjusted Breast Cancer–Specific Mortality for SEER-Medicare Patients



Adjusted breast cancer–specific mortality for Surveillance, Epidemiology, and End Results (SEER)-Medicare patients for preoperative delay intervals of ≤60, 61-120, and 121-180 days. A, Subdistribution hazard ratio (sHR) was 1.26 for all stages combined (95% CI, 1.02-1.54; $P = .03$); B, 1.84 for stage I (95% CI 1.10-3.07, $P = .02$); C, 1.03 for stage II (95% CI, 0.83-1.28; $P = .80$); and D, 1.04 for stage III (95% CI, 0.82-1.33; $P = .74$). For the comparison of stage I sHR with stage II and stage III sHRs, $P = .04$ and $P = .06$, respectively.

Table 2. Point Estimates for Adjusted Overall Survival for Each Study by Surgery Interval Delay

	Surgery Delay, d									
	≤30		31-60		61-90		91-120		121-180	
Years	No. at Risk	AOS (95% CI)[a]	No. at Risk	AOS (95% CI)[a]	No. at Risk	AOS (95% CI)[a]	No. at Risk	AOS (95% CI)[a]	No. at Risk	AOS (95% CI)[a]
SEER-Medicare Database Study										
5	38 075	78.1 (77.7-78.4)	6370	77.9 (77.0-78.8)	760	73.5 (70.4-76.7)	235	73.5 (66.4-80.5)	121	60.9 (50.5-71.3)
10	10 870	54.2 (53.7-54.7)	1132	53.2 (51.7-54.7)	110	47.1 (41.3-52.9)	24	45.0 (33.7-56.3)	16	40.2 (27.7-52.7)
15	2386	32.7 (32.0-33.4)	212	29.3 (26.7-31.9)	12	21.7 (13.7-29.7)	<11	14.9 (2.1-27.7)	<11	26.0 (9.0-43.1)
National Cancer Database Study										
5	60 909	88.0 (87.7-88.2)	21 464	87.5 (87.1-87.9)	3269	85.4 (84.1-86.7)	746	84.9 (81.9-87.9)	359	80.4 (75.4-85.5)

Abbreviations: AOS, adjusted overall survival estimate; numbers less than 11 are not reported, per National Cancer Insititute Surveillance, Epidemiology, and End Results (SEER)-Medicare guidelines.

[a] All AOS values reported as percentages.

vs II disease; $P < .001$ for stage I vs III; and $P = .04$ for stage II vs III. The HRs and sHRs are listed in eTable 3 in the Supplement. Cause-specific mortality is not available for the NCDB data set. Mean (SD) follow-up among those who did not die was 6.00 (1.80) years. Subgroup point estimates for 5-year OS are listed in Table 2.

Table 3. Adjusted/Weighted and Unadjusted/Unweighted Patient and Tumor Characteristics From the NCDB Study by Surgery Delay Interval[a]

	Time to Surgery Interval, d				
Characteristic	≤30	31-60	61-90	91-120	121-180
Total patients, No.	80 505	28 832	4697	1152	604
Mean age, y	60.4 (60.1)	60.5 (60.8)	60.9 (60.8)	60.6 (60.7)	60.3 (61.3)
Sex					
Female	99.1 (99.0)	99.1 (99.3)	98.7 (99.3)	NR[b]	NR[b]
Male	0.9 (1.0)	0.9 (0.7)	1.3 (0.7)	NR[b]	NR[b]
Race					
White	82.8 (85.4)	82.9 (79.6)	82.4 (71.0)	80.7 (58.5)	85.0 (57.0)
Black	9.2 (7.6)	9.1 (11.2)	9.2 (16.7)	9.6 (23.1)	8.5 (26.0)
Asian	2.1 (2.0)	2.2 (2.3)	2.3 (2.4)	2.2 (3.0)	1.7 (3.8)
Hispanic	4.1 (3.2)	4.0 (5.1)	4.1 (8.2)	5.0 (12.5)	3.5 (10.8)
Other/unknown	1.8 (1.8)	1.8 (1.8)	1.9 (1.8)	2.5 (2.9)	1.4 (2.5)
Charlson Comorbidity Index[c]					
0	88.1 (88.8)	88.1 (87.4)	87.9 (85.6)	86.9 (84.2)	88.0 (83.6)
1	10.0 (9.6)	10.1 (10.5)	10.0 (11.4)	10.9 (11.9)	10.0 (12.4)
≥2	1.8 (1.7)	1.9 (2.1)	2.1 (3.0)	2.3 (3.9)	2.0 (4.0)
Setting[d]					
Large metropolitan	51.3 (47.9)	51.2 (57.9)	51.3 (63.1)	52.9 (67.5)	46.9 (68.9)
Metropolitan	32.6 (34.5)	32.7 (29.1)	32.5 (25.8)	30.9 (23.0)	35.2 (21.5)
Urban	6.5 (7.0)	6.5 (5.6)	6.3 (4.9)	6.3 (3.8)	7.6 (4.3)
Less urban/rural	9.6 (10.7)	9.6 (7.5)	9.9 (6.2)	9.9 (5.6)	10.3 (5.3)
Invasive histologic finding					
Ductal	89.2 (89.5)	89.3 (88.7)	88.9 (88.6)	87.4 (87.7)	87.9 (87.3)
Lobular	8.1 (7.7)	8.1 (8.7)	8.0 (8.6)	9.5 (9.6)	9.7 (8.9)
Other/unknown	2.7 (2.8)	2.7 (2.6)	3.2 (2.8)	3.1 (2.8)	2.4 (3.8)
Grade					
Well differentiated	21.0 (20.4)	21.0 (22.5)	20.9 (22.5)	21.4 (18.4)	19.7 (17.7)
Moderately differentiated	39.7 (39.4)	39.8 (40.3)	40.1 (40.5)	42.9 (43.0)	40.9 (35.6)
Poorly differentiated	32.6 (33.8)	32.5 (30.2)	31.9 (28.9)	29.0 (29.9)	32.8 (33.8)
Undifferentiated/ anaplastic	0.9 (0.9)	0.8 (0.8)	0.9 (1.0)	0.6 (1.7)	0.5 (2.3)
Unknown	5.8 (5.5)	5.9 (6.2)	6.3 (7.1)	6.1 (7.0)	6.1 (10.6)
Mean tumor size, cm	2.1 (2.1)	2.0 (2.0)	2.1 (2.1)	2.1 (2.1)	2.2 (3.4)
AJCC stage[e]					
I	52.1 (51.6)	52.2 (53.6)	51.9 (52.1)	50.2 (50.4)	48.0 (41.6)
II	37.2 (37.6)	37.0 (36.3)	37.2 (35.6)	39.3 (34.9)	40.4 (38.9)
III	10.8 (10.7)	10.8 (10.1)	11.0 (12.4)	10.5 (14.7)	11.7 (19.5)
Surgical margins: residual tumor					
None	94.6 (94.8)	94.6 (94.4)	94.3 (93.6)	94.6 (91.1)	95.6 (92.4)
Residual	4.3 (4.2)	4.3 (4.3)	4.7 (4.6)	4.2 (6.4)	3.3 (4.8)
Other/unknown	1.1 (1)	1.1 (1.3)	1.1 (1.8)	1.2 (2.5)	1 (2.8)
Nodes examined, mean No.	7.8 (7.8)	7.8 (7.7)	7.8 (8.2)	7.8 (8.7)	8.5 (9.4)
Positive nodes, mean No.	1.2 (1.2)	1.2 (1.1)	1.2 (1.3)	1.2 (1.4)	1.4 (1.9)
Surgery type					
Breast conservation	62.9 (65.4)	63 (58.9)	63.7 (51.9)	60.3 (48.2)	64.4 (45.5)
Mastectomy	37.1 (34.6)	37 (41.1)	36.3 (48.1)	39.7 (51.8)	35.6 (54.5)
Chemotherapy use					
Yes	37.1 (34.6)	37 (41.1)	36.3 (48.1)	39.7 (51.8)	35.6 (54.5)
No	62.9 (65.4)	63 (58.9)	63.7 (51.9)	60.3 (48.2)	64.4 (45.5)
Radiotherapy use					
Yes	62.8 (65.5)	62.7 (58.7)	63.3 (50.6)	60.4 (44.8)	65.4 (40.9)
No	37.2 (34.5)	37.3 (41.3)	36.7 (49.4)	39.6 (55.2)	34.6 (59.1)

(continued)

Table 3. Adjusted/Weighted and Unadjusted/Unweighted Patient and Tumor Characteristics From the NCDB Study by Surgery Delay Interval[a] (continued)

Characteristic	Time to Surgery Interval, d				
	≤30	31-60	61-90	91-120	121-180
Endocrine therapy use					
Yes	52.5 (53.1)	52.5 (52.8)	51.5 (48)	51.7 (43.1)	53.5 (36.6)
No	47.5 (46.9)	47.5 (47.2)	48.5 (52)	48.3 (56.9)	46.5 (63.4)
Insurance type					
None	2.0 (1.8)	2.0 (2.2)	2.0 (3.3)	1.9 (5.1)	1.9 (5.5)
Private	16.5 (17.8)	16.5 (13.9)	16.6 (12.1)	17.2 (10)	17.6 (9.6)
Managed care	39.2 (39.2)	39 (40.6)	37.1 (36.5)	38.3 (33.9)	36.4 (30.1)
Medicaid	4.3 (3.5)	4.3 (5.2)	4.6 (8.2)	4.8 (11.1)	4.5 (10.9)
Medicare	35 (34.6)	35.3 (35.4)	37.2 (35.7)	35.5 (33.5)	38.1 (36.9)
Other government/ unknown	3.0 (3.0)	2.9 (2.7)	2.4 (4.2)	2.4 (6.3)	1.6 (7.0)

Abbreviations: AJCC, American Joint Committee on Cancer; NCDB, National Cancer Database; NR, not reported.

[a] Unless otherwise indicated, data are reported as adjusted (unadjusted) percentages of patients; totals may vary from 100% due to rounding. Variables included in the analysis but not displayed in this table for reasons of space are region, income, education, year of diagnosis, facility/cancer program type, mean distance to facility, and analytic case type; these variables are delineated in eTable 5 in the Supplement.

[b] Cells have been deleted per NCDB requirements to censor cells containing fewer than 11 individuals or other cells that make such cells calculable.

[c] Charlson scores of 2 or higher are collapsed together into a single group, and so mean Charlson scores for NCDB data cannot be calculated.

[d] Setting definitions: Large metropolitan indicates counties of metropolitan areas of 1 million population or more; metropolitan, counties in metropolitan areas up to 1 million population; urban, urban population of 20 000 or more adjacent or nonadjacent to a metropolitan area; less urban, urban population of 2500-19 999 adjacent or nonadjacent to a metropolitan area; rural, completely rural or less than 2500 urban population adjacent or nonadjacent to a metropolitan area.

[e] In determining AJCC stage the third and sixth AJCC editions were combined; substages (eg, IIA, IIB) were collapsed to minimize differences between editions.

Discussion

Although the relationship between TTS and breast cancer outcomes might be assumed to be a modern health care concern, admonition about breast cancer treatment delays first occurred over 100 years ago[1] with TTS at that time measured in months rather than days or weeks.[15] Until recently, there have been little data about waiting times in the United States,[5,16] and there remains little consensus about the relationship between delays and survival.

Although no data set can determine every cause of delay, especially those on the part of the patient, we have noted that some factors increase in prevalence as preoperative delays increase. Our research group has previously found that multiple factors correlate with a longer time to breast cancer surgery,[5] but regardless of the cause, when adjusting for these and numerous other demographic, tumor, and treatment factors, we found that delays still independently correlated with a slightly lower survival rate in both the SEER-Medicare and NCDB cohorts.

We have found that OS declines when the TTS increases, with OS affected in stage I and II but not stage III disease. The data for DSS are similar, with cancer-specific mortality data only available in the SEER-Medicare dataset, where patients with stage I cancer exhibited lower survival as TTS increased. This observation that preoperative delays affected only stage I DSS and stage I and stage II OS could be due to lower numbers of patients with higher-stage disease, but we believe that breast cancer survivability in its earliest stage is more influenced by the TTS than it is in later stages because baseline mortality is smaller relative to the effect imposed by a delay in treatment. In both cohorts, OS and DSS for stage III disease were not influenced by TTS, suggesting either partial biologic predestination of outcome or a mortality risk that overshadows any small effect of reducing delay by a matter of months. This effect may also be attenuated by patient age owing to competing mortality risks. Because of this and because final stage is only available postoperatively, we believe that efforts to minimize preoperative delay for all patients is advisable.

We have adjusted for numerous variables in each study, but unmeasured confounders could still exist, as with every series, affecting survival negatively or positively. We excluded patients having neoadjuvant chemotherapy in these analyses to maintain cohort homogeneity and because we found that these patients had a markedly longer TTS because of the lengthy time imposed by the treatment itself, with lower survival related to its indications, skewing the data toward the appearance of artificially worse outcomes with longer delays. The slight differences we see in the magnitude of effect by delay for the SEER-Medicare vs NCDB cohort may reflect the complexities in the relationship between age and tumor biology,[17] or age and treatment,[18] that cannot be clearly defined in these data sets. It also must be recognized that the effects seen here may result from delay to surgery, delay to postoperative therapy, or both. For patients for whom surgery is the first treatment before systemic therapy, these possibilities are inextricable, and all underscore the need to avoid undue delay.

The effect of TTS on survival is a ubiquitous concern of patients with cancer and a question frequently posed in consultations with surgeons. Elimination of undue delay is desirable to both reduce anxiety and lower risk, and we believe that this study provides clinicians needed data to answer patients' questions about TTS and its effect on outcome. While

the absolute magnitude of the 5-year survival difference was small (4.6% and 3.1% for ≤30 days vs 91-120 days in SEER-Medicare and NCDB patients, respectively), this benefit is comparable to the addition of some standard therapies, such as the recent extension of tamoxifen therapy from 5 to 10 years,[19] while not having the adverse effects or costs found with most interventions.

Whether TTS should be revisited as a quality measure could be debated in light of practical matters that contribute to delay. Some of these are patient driven, such as the desire for multiple opinions, limitations in the patient's schedule, or not seeking care as instructed. Some may be system driven, such as a lack of available operating room time, appointment times, insurance issues, and barriers to care. Yet others may be physician related, such as schedule limitations or excessive use of imaging or other testing. The National Quality Forum, National Comprehensive Cancer Network, and American Society of Clinical Oncology have already ratified at least 3 time-dependent breast cancer measures.[20] These include receipt of tamoxifen or an aromatase inhibitor within 1 year of diagnosis, initiation of breast radiotherapy within 1 year of diagnosis, and receipt of adjuvant chemotherapy within 4 months of diagnosis.

Questions remain as to whether time-dependent measures improve the quality of care,[21] but there has already been consideration of TTS as a quality measure.[2-4] The previous lack of clear data has weakened the need for such a standard, but our findings here suggest that a reasonable delay threshold might be appropriate for oncologic surgery, as it has been for medical oncology and radiation oncology. Because only 1.2% and 1.5% of the SEER-Medicare and NCDB patients, respectively, had a TTS that was over 90 days, providing these few patients with breast cancer the 3% to 5% survival benefit associated with reduced delay also seems achievable.

Unfortunately, prior studies on survival and delay have been inconclusive. While some suggest that these factors are linked,[22-24] others have found no correlation.[25-27] Many select an arbitrary single-interval cutoff at which delay is defined.[23,24,26] In our 2 series, the cohort sizes provided power beyond that achieved by prior analyses and allowed for analysis of multiple delay groups of varying lengths while adjusting for numerous confounders to clarify the relationship. The similar results between separate analyses of these 2 large national data sets, having different characteristics, is also compelling and suggests that the effect of delay on survival is a true phenomenon and not one specific to a particular cohort.

Although this report describes 2 population-based series, a prospective study randomizing patients to varying degrees of delay is unlikely to occur because of both ethical considerations and aversion to delays in treatment. For this reason, we believe that these analyses of 2 of the largest prospectively collected data sets in existence for the United States provide the most definitive demonstration possible. The 15-year estimates and the 120- to 180-day estimates show a larger benefit of minimizing delay, but these subgroups also have very few individuals at risk, limiting the power of even these large analyses.

Conclusions

In conclusion, survival outcomes in early-stage breast cancer are affected by the length of the interval between diagnosis and surgery, and efforts to minimize that interval are appropriate. Although the effect on both overall and disease-specific survival remains small, consideration should be given to establishing reasonable and attainable goals for the timing of surgical interventions to afford this population a finite, but clinically relevant, survival benefit.

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