A Reappraisal of the Comparative Effectiveness of Lumpectomy Versus Mastectomy on Breast Cancer Survival: A Propensity Score–Matched Update From the National Cancer Data Base (NCDB)

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Abstract

In a propensity score–matched investigation of more than 800,000 patients with breast cancer in the National Cancer Database, the effect of surgery type (lumpectomy vs. mastectomy) on overall survival was dependent on cancer stage and hormone receptor status.

Background: Recent observational studies are concerning because they document rising mastectomy rates coinciding with more than a dozen reports that lumpectomy has better overall survival (OS) than mastectomy. Our aim was to determine if there were differences in OS of matched breast cancer patients undergoing lumpectomy versus mastectomy in the National Cancer Database (NCDB). **Patients and Methods:** A retrospective cohort of patients with stage I-III breast cancer in the NCDB (2004-2013) was identified. Propensity score matching (PSM), Kaplan-Meier, and multivariate Cox proportional hazards models were used to examine OS by type of surgery. **Results:** Of 845,136 patients, 464,052 (54.9%) underwent lumpectomy and 381,084 (45.1%) underwent mastectomy. After PSM, the hazard ratio (HR) and confidence interval (CI) for OS in all patients comparing lumpectomy with mastectomy was 1.02 (CI, 1.00-1.04; $P = .002$). In patients with stage I, II, and III, they were HR 1.27 (CI, 1.23-1.36; $P < .001$), HR 0.98 (CI, 0.95-1.01; $P = .21$), and HR 0.83 (CI, 0.80-0.86; $P < .001$), respectively. In subgroup analyses of all patients by estrogen receptor (ER) status, they were HR 1.05 (CI, 1.03-1.07; $P < .001$) and HR 1.00 (CI, 0.96-1.03; $P = .65$) in ER+ and ER− patients. **Conclusion:** In our primary model of all stage I-III matched patients, using the most recent NCDB data and the largest observational sample size to date, the OS after mastectomy was not inferior to lumpectomy. This finding can be reassuring to patients and providers. In subgroup analyses, the association between type of surgery and OS differed by cancer stage and hormone receptor status.

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Introduction

Decades ago, multiple randomized trials demonstrated equivalency of overall survival (OS) between those patients with breast cancer undergoing breast-conserving surgery (BCS) compared with those undergoing mastectomy.[1-11] In contrast, 14 recent observational investigations reported a different conclusion.[12-25] In these studies, patients undergoing BCS had a better cancer outcome than those undergoing mastectomy. This discordance between trials and observational data has been noted but not yet reconciled.[26] Given that mastectomy rates have risen during the past decade, the finding that cancer outcomes may be better with BCS is concerning.[12,13,26]

Breast cancer treatments have changed and the number of patients captured in the National Cancer Database (NCDB) has increased fourfold since the dates of the studies cited in the

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preceding paragraph. Consequently, using the NCDB, we sought to evaluate OS in those patients exposed to lumpectomy compared with matched patients exposed to mastectomy, aiming to inform and update patient and provider stakeholders. We hypothesized there would be no significant difference in OS by type of surgery.

Patients and Methods

The NCDB is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society.[27] The hospitals participating in the NCDB are the source of the de-identified data; they have not verified and are not responsible for the validity of the data analysis or the conclusions derived by the authors.[27] The Patient User Files were de-identified. The study was considered exempt for review by our institutional review board.

Study Population

Patients were female gender, > 17 years of age, with pathologic stage I-III breast cancer who underwent any type of BCS or mastectomy from 2004 to 2013. Patients were excluded for the following: receipt of neo-adjuvant radiation, no receipt or unknown type/date of surgery or tumor size, unknown vital status for OS or time to last contact, non-primary breast cancer histologic codes, prior cancer diagnosis, bilateral cancer, or surgery more than 6 months after diagnosis (Figure 1). For any patient with a missing value for an adjustment variable, an "unknown value" category was created for that variable and the patient included.

Predictor Variables

Exposures of interest were "definitive" BCS (NCDB lumpectomy codes 20-22, 24) and mastectomy (codes 30, 40- 80, except 76). Patients with lumpectomy followed by mastectomy and with bilateral mastectomy were classified as mastectomy.

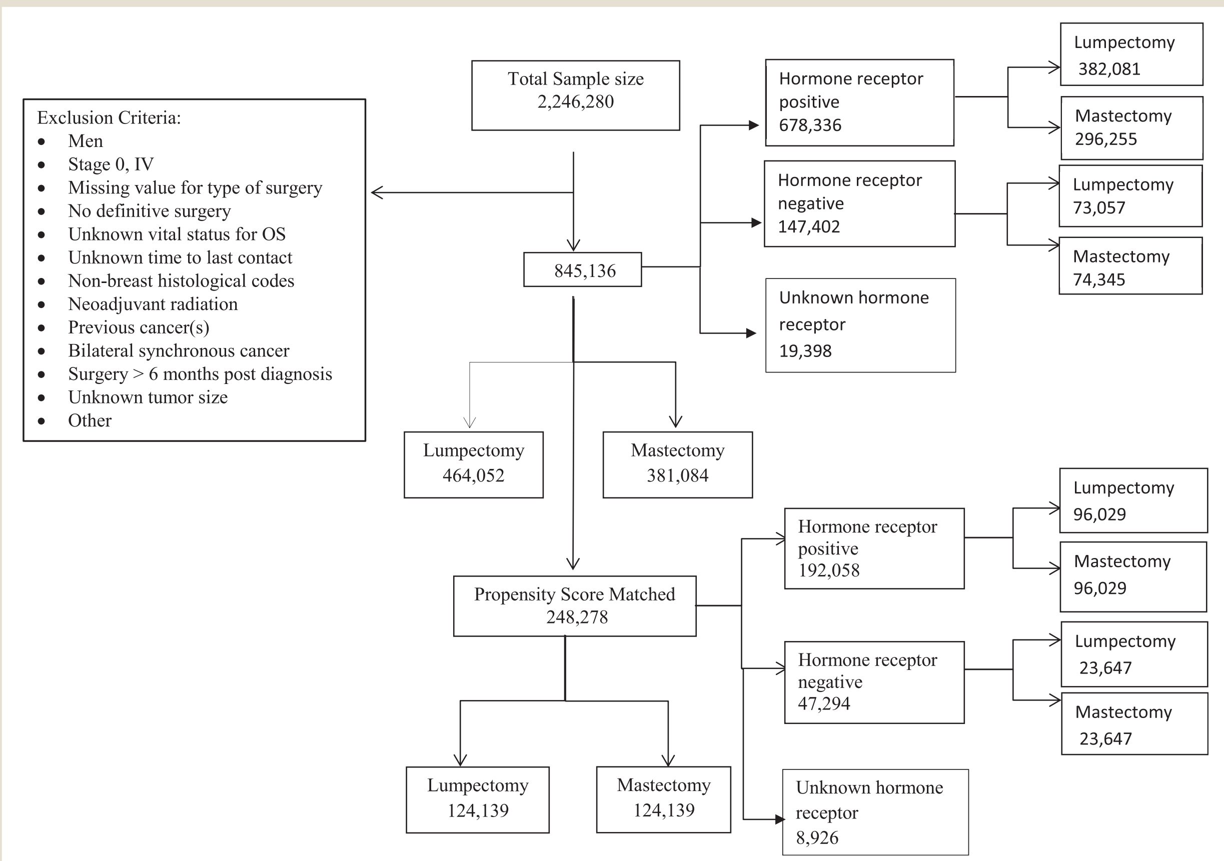
Study Covariates

The adjustment variables included patient, facility, tumor, and treatment characteristics, year and time from diagnosis to first treatment (Table 1).

Dependent Variable

OS was the outcome of interest, defined as the time from diagnosis to date of death or last follow-up. Patients who did not die were censored at the date of last follow-up. To meet the NCDB standards for reporting, a facility must track survival status for 90% and 80% of analytic cases for 5 years and for longer, respectively.

Figure 1 Flow Diagram of National Cancer Data Base Stage I-III Breast Cancer Patients From 2004 to 2013



Abbreviation: OS = overall survival.

Table 1 Univariate Analysis of Patient, Facility, Tumor and Treatment Characteristics by Type of Surgery in Patients With Stage I-III Breast Cancer

Patients (N = 845,136)						
	Lumpectomy		Mastectomy			
	n = 464,052 (54.9%)		n = 381,084 (45.1%)		Total	
Characteristics	n	%	n	%	n	*P*
Patient						
Age, y						
<40	12,915	33.3	25,899	66.7	38,814	<.001
40-49	71,857	46.0	84,247	54.0	156,104	
50-59	1207,95	55.8	95,869	44.2	216,664	
60-70	142,486	60.8	91,740	39.2	234,226	
>80	115,999	58.2	83,329	41.8	199,328	
Race						
White	396,187	55.3	320,529	44.7	716,716	<.001
Black	46,968	54.1	39,823	45.9	86,791	
Other	16,118	48.6	17,034	51.4	33,152	
Missing/Unknown	4779	56.4	3698	43.6	8477	
Comorbidity score						
0	400,632	55.7	318,399	44.3	719,031	<.001
1	53,122	51.0	51,084	49.0	104,206	
2	10,298	47.0	11,601	53.0	21,899	
Payer						
Not insured	7634	47.4	8476	52.6	16,110	<.001
Private insurance/ managed care	252,743	54.2	213,760	45.8	466,503	
Medicaid	21,737	46.6	24,877	53.4	46,614	
Medicare	170,897	58.2	122,706	41.8	293,603	
Other government	4006	51.2	3821	48.8	7827	
Insurance status unknown	7035	48.6	7444	51.4	14,479	
Income						
Less than $38,000	63,687	51.2	60,719	48.8	124,406	<.001
$38,000-$47,999	97,626	53.7	84,074	46.3	181,700	
$48,000-$62,999	124,491	55.2	100,869	44.8	225,360	
$63,000 +	174,163	56.9	131,826	43.1	305,989	
Missing/Unknown	4085	53.2	3596	46.8	7681	

Table 1 Continued

Patients (N = 845,136)	Lumpectomy		Mastectomy		Total	
	n = 464,052 (54.9%)		n = 381,084 (45.1%)			
Characteristics	n	%	n	%	n	*P*
No High School level of education						
21% or more	61,947	51.2	59,124	48.8	121,071	<.001
13%-20.9%	106,539	53.4	92,979	46.6	199,518	
7%-12.9%	155,514	55.9	122,720	44.1	278,234	
Less than 7%	136,160	57.0	102,847	43.0	239,007	
Missing/Unknown	3892	53.3	3414	46.7	7306	
County type						
Rural	2939	43.5	3816	56.5	6755	<.001
Urban area	56,032	51.4	52,963	48.6	108,995	
Metro area	390,775	55.5	313,371	44.5	704,146	
Missing/Unknown	14,306	56.7	10,934	43.3	25,240	
Facility						
Facility location						
New England	30,859	65.4	16,317	34.6	47,176	<.001
Middle Atlantic	68,799	60.0	45,827	40.0	114,626	
South Atlantic	102,075	55.4	82,139	44.6	184,214	
East North Central	84,846	57.8	61,915	42.2	146,761	
East South Central	24,312	46.4	28,033	53.6	52,345	
West North Central	31,102	50.3	30,777	49.7	61,879	
West South Central	30,183	48.2	32,375	51.8	62,558	
Mountain	21,069	54.9	17,332	45.1	38,401	
Pacific	57,892	58.9	40,470	41.1	98,362	
Missing/Unknown	12,915	33.3	25,899	66.7	38,814	
Facility type						
Community cancer program	12,915	33.3	25,899	66.7	38,814	<.001
Comprehensive community cancer program	50,452	55.7	40,093	44.3	90,545	
Academic/research program	222,120	56.3	172,308	43.7	394,428	

Table 1 Continued

Patients (N = 845,136)						
	Lumpectomy		Mastectomy		Total	
	n = 464,052 (54.9%)		n = 381,084 (45.1%)			
Characteristics	**n**	**%**	**n**	**%**	**n**	***P***
Integrated network cancer program	128,925	55.6	102,921	44.4	231,846	
Other or unknown types of cancer programs	49,640	55.5	39,863	44.5	89,503	
Tumor						
Hormone receptor status						
Negative	73,057	49.6	74,345	50.4	147,402	<.001
Positive	382,081	56.3	296,255	43.7	678,336	
Missing/Unknown	8914	46.0	10,484	54.0	19,398	
Grade						
Poorly/Undifferentiated	129,351	48.2	139,257	51.8	268,608	<.001
Moderately differentiated	194,169	54.9	159,262	45.1	353,431	
Well differentiated	116,987	66.0	60,356	34.0	177,343	
Not Determined	23,545	51.5	22,209	48.5	45,754	
Histology						
Ductal	396,371	57.1	297,229	42.9	693,600	<.001
Lobular	34,495	42.4	46,835	57.6	81,330	
Other	33,186	47.3	37,020	52.7	70,206	
AJCC Pathologic T						
0	564	31.7	1213	68.3	1777	<.001
1	25,815	62.0	15,803	38.0	41,618	
1A	36,137	62.3	21,873	37.7	58,010	
1B	103,863	72.3	39,706	27.7	143,569	
1C	185,090	64.1	103,877	35.9	288,967	
1MI	6119	48.5	6509	51.5	12,628	
2	100,581	40.8	146,088	59.2	246,669	
3	3727	10.0	33,605	90.0	37,332	
4	290	12.1	2105	87.9	2395	
4A	160	18.8	691	81.2	851	
4B	622	10.4	5344	89.6	5966	
4C	36	11.4	281	88.6	317	

Table 1 Continued

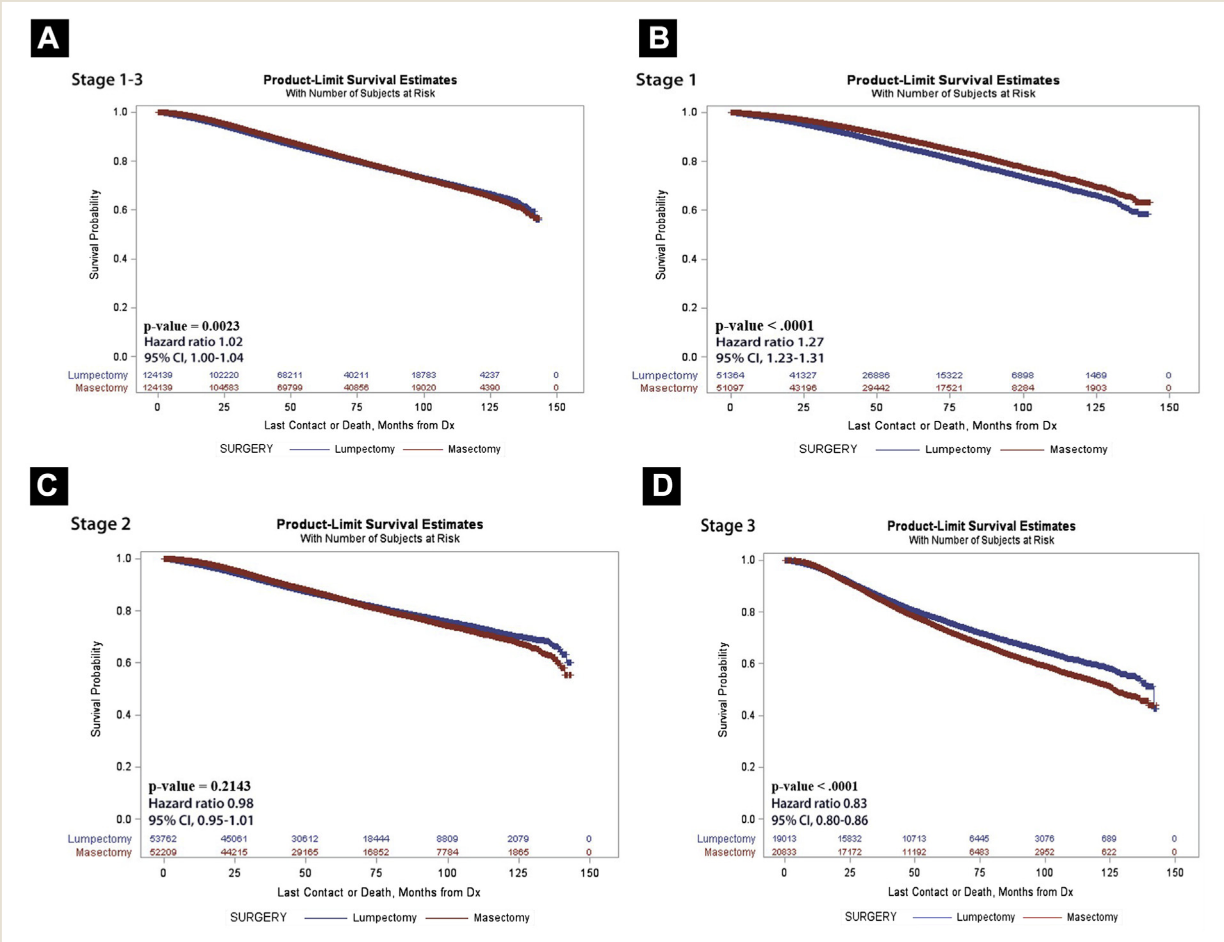
Patients (N = 845,136)	Lumpectomy n = 464,052 (54.9%)		Mastectomy n = 381,084 (45.1%)		Total	
Characteristics	n	%	n	%	n	*P*
4D	98	4.2	2243	95.8	2341	
Missing/Unknown	207	36.5	360	63.5	567	
X	743	34.9	1386	65.1	2129	
AJCC Pathologic N						
0	351,615	63.7	200,439	36.3	552,054	<.001
0+	6879	47.4	7630	52.6	14,509	
1	26,490	42.9	35,269	57.1	61,759	
1A	38,132	40.3	56,456	59.7	94,588	
1B	542	40.5	795	59.5	1337	
1C	337	33.9	657	66.1	994	
1MI	11,827	48.4	12,630	51.6	24,457	
2	3967	25.7	11,461	74.3	15,428	
2A	9231	24.3	28,793	75.7	38,024	
2B	102	27.1	274	72.9	376	
3	1364	18.7	5912	81.3	7276	
3A	3224	18.3	14,359	81.7	17,583	
3B	145	18.5	638	81.5	783	
3C	125	27.1	337	72.9	462	
Missing/Unknown	1211	66.5	610	33.5	1821	
X	8861	64.7	4824	35.3	13,685	
Margin status						
Margins not evaluable	4288	41.5	6039	58.5	10,327	<.001
Negative	439,278	55.0	359,178	45.0	798,456	
Positive	20,486	56.4	15,867	43.6	36,353	
Adjuvant treatment receipt						
Chemotherapy						
Yes	170,028	45.2	206,390	54.8	376,418	<.001
No	280,317	63.1	164,052	36.9	444,369	
Missing/Unknown	13,707	56.3	10,642	43.7	24,349	
Hormone therapy						

Table 1 Continued

Patients (N = 845,136)						
	Lumpectomy		**Mastectomy**			
	n = 464,052 (54.9%)		**n = 381,084 (45.1%)**		**Total**	
Characteristics	**n**	**%**	**n**	**%**	**n**	***P***
Yes	307,273	56.6	235,813	43.4	543,086	<.001
No	139,167	51.5	131,200	48.5	270,367	
Missing/Unknown	17,612	55.6	14,071	44.4	31,683	
Radiation treatment						
Beam/Implants/Not otherwise specified	395,795	79.3	103,538	20.7	499,333	<.001
Radioisotopes	234	97.5	6	2.5	240	
None	63,927	19.1	270,241	80.9	334,168	
Missing/Unknown	4096	35.9	7299	64.1	11,395	
Year of diagnosis						
2004	39,286	54.4	32,994	45.6	72,280	<.001
2005	41,269	55.6	32,953	44.4	74,222	
2006	43,251	55.8	34,329	44.2	77,580	
2007	43,808	54.6	36,362	45.4	80,170	
2008	44,220	53.8	37,987	46.2	82,207	
2009	45,931	53.8	39,373	46.2	85,304	
2010	47,077	53.9	40,316	46.1	87,393	
2011	51,545	55.1	42,026	44.9	93,571	
2012	52,766	54.6	43,814	45.4	96,580	
2013	54,899	57.3	40,930	42.7	95,829	
Time for the diagnosis to the first treatment						
Days from diagnosis						
Minimum	0		0			<.001
25th percentile	14		14			
Median	24		26.5			
75th percentile	36		42			
Maximum	182		201			

Abbreviation: AJCC = American Joint Committee on Cancer.

Figure 2 Overall Survival Curves by Type of Surgery and Stage in Propensity Score−matched Patients With Breast Cancer. (A) Overall Survival Stage 1-3 by Type of Surgery. (B) Overall Survival Stage 1 by Type of Surgery. (C) Overall Survival Stage 2 by Type of Surgery. (D) Overall Survival Stage 3 by Type of Surgery



Abbreviation: Dx = diagnosis.

Analysis

Baseline characteristics for each of the independent variables across treatment groups were compared by univariate analysis using Pearson χ^2 for categorical and *t* tests for continuous variables. Univariate (UV), multivariate (MV), and propensity score−matched (PSM) models were used to determine associations between type of surgery and OS. In matched patients, Kaplan-Meier curves were used to visualize OS for the entire group of patients and subgroups. A multivariate Cox proportional hazards regression model, using all the adjustment variables in Table 1, was used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) for OS.

In the PSM model, the propensity scores were estimated probabilities of patients receiving mastectomy based on the independent variables in Table 1, except final margin status, as it was not known preoperatively. Construction of the PSM of mastectomy receipt used a stepwise variable selection process in which a *P* value < .05 was required for both initial and continued inclusion of each potential covariate in the model. Mastectomy and lumpectomy patients were matched 1:1 on propensity score, with a maximum allowed difference in propensity score of ±2%, calculated by logistic regression. Planned subgroup analyses of matched patients were performed by fitting separate models for estrogen and/or progesterone receptor status (hereafter referred to as ER+ or ER−) and stage.

P values were 2 sided. *P* values < .05 were considered significant.

Statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

Literature Review of Observational Studies

A comprehensive, but not a systematic, review of the observational literature (2000-2018) was performed with the search terms breast cancer, type of surgery, mastectomy, lumpectomy, BCS, OS, and survival in all combinations. After review, publications were excluded for a sample size of fewer than 5000 patients, inclusion of stage 0, ER status/age restricted, overlapping patients in separate reports, meta-analyses, and randomized trials.

Table 2 Comparative Effectiveness of Lumpectomy Versus Mastectomy (Reference) on 10- year Overall Survival in Stage I-III Patients by Univariate, Multivariate, and Propensity Score−Matched Analyses

				Survival Rate[a]		Analysis					
						Univariate (n = 845,136)		Multivariate[b] (n = 845,136)		Propensity Score Matched (n = 248,278)	
Model	**Surgery**	**No. of Patients**	**No. of Deaths**	**5-Year (%)**	**10-Year (%)**	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
All patients	Lumpectomy	464,052	51,677	90.7	77.5	0.62 (0.61-0.62)	<.001	1.11 (1.09-1.13)	<.001	1.02 (1.00-1.04)	.002
	Mastectomy	381,084	64,747	84.5	68.3	1 (Ref)		1 (Ref)		1 (Ref)	
Hormone receptor positive[c]	Lumpectomy	382,081	38,227	91.9	78.2	0.64 (0.63-0.65)	<.001	1.13 (1.11-1.15)	<.001	1.05 (1.03-1.07)	<.001
	Mastectomy	296,255	43,923	87.0	69.6	1 (Ref)		1 (Ref)		1 (Ref)	
Hormone receptor negative[d]	Lumpectomy	73,057	11,944	85.0	74.2	0.59 (0.58-0.60)	<.001	1.06 (1.03-1.09)	<.001	1.00 (0.96-1.03)	.65
	Mastectomy	74,345	18,586	75.2	63.0	1 (Ref)		1 (Ref)		1 (Ref)	

[a]Unadjusted.
[b]Cox proportional hazards regression model.
[c]Estrogen receptor (ER)+ and/or progesterone receptor (PR)+.
[d]ER− and PR−.

Table 3 Comparative Effectiveness of Lumpectomy Versus Mastectomy (Reference) on 10- year Overall Survival by Stage and Hormone Receptor Status in Stage I-III Patients After Propensity Score Matching

Patient Cohort	Lumpectomy 10-Year OS (%)	Mastectomy 10-Year OS (%)	Hazard Ratio	CI		*P*
Stage I-III patients, any ER/PR status						
Stage I	67.5	71.4	1.27	1.23	1.31	<.001
Stage II	71.1	69.2	0.98	0.95	1.01	.21
Stage III	59.5	52.7	0.83	0.80	0.86	<.001
Stage I-III patients, ER and/or PR positive						
Stage I	66.7	71.1	1.31	1.26	1.35	<.001
Stage II	72.2	69.9	0.98	0.94	1.02	.36
Stage III	61.8	55.8	0.82	0.78	0.86	<.001
Stage I-III patients, ER and PR negative						
Stage I	71.6	72.0	1.21	1.11	1.31	<.001
Stage II	66.2	66.6	0.99	0.94	1.04	.90
Stage III	51.2	47.7	0.89	0.83	0.95	.002

Abbreviations: ER = estrogen receptor; OS = overall survival; PR = progesterone receptor.

Results

In the UV and MV analyses, there were 845,136 patients (lumpectomy 464,052 [54.9%]; mastectomy 381,084 [45.1%]). In the PSM model, there were 248,278 patients (lumpectomy 124,139 [50.0%]; mastectomy 124,139 [50.0%]).

The mean (standard deviation), median, and range of dates (months) to last contact or death were 61 (34), 57, and 0-147 in the total patient cohort before PSM.

The frequencies and association of all independent variables with type of surgery are shown in Table 1.

Survival

The 10-year unadjusted OS for all patients (stage 1-3) treated by lumpectomy and mastectomy was 77.5% (CI, 77.2%-77.7%) and 68.3% (CI, 68.0%-68.5%; $P < .001$) respectively. Adjusted survival curves by stage after PSM are shown in Figure 2. The HRs comparing lumpectomy with mastectomy (reference) in the UV, MV, and PSM models were 0.62 (CI, 0.61-0.62; $P < .001$), 1.11 (CI, 1.09-1.13; $P < .001$), and 1.02 (CI, 1.00-1.04; $P = .002$) (Table 2).

Survival analyses (PSM) by stage and ER status are shown in Tables 2 and 3 and Figure 2.

Comprehensive Review of Literature

From 2783 titles, 50 articles were reviewed. Fourteen were relevant to our objective.[12-25] Differences in their study design and findings are described in the discussion that follows.

Discussion

In 1898, William Halsted[28] reported on a patient who underwent a radical mastectomy. Since that date, less-radical mastectomies were performed, but most surgeons did not embrace partial mastectomy until Bernard Fisher and colleagues[1] and Umberto Veronesi and colleagues[3] published their seminal randomized trials 3 decades ago. These trials demonstrated no difference in OS between those patients with breast cancer undergoing lumpectomy compared with those undergoing mastectomy.[2,4] Soon thereafter, the National Institutes of Health endorsed lumpectomy as the "preferred" local treatment for breast cancer instead of mastectomy.[29] As a result, rates of BCS increased during the next 2 decades. More recently, especially in the United States, these rates have declined.[12,30] BCS rates peaked at 70% in the years 2004-2006.[30]

The recent increase in mastectomy rates coincides with observations of mastectomy "disadvantage." In more than a dozen reports, including 4 that used the NCDB and Surveillance, Epidemiology, and End Results (SEER), those patients undergoing BCS had better OS than those undergoing mastectomy.[12-25] In contrast, randomized trials identified equivalency, not superiority of BCS over mastectomy.[1-11] The reason for this difference between trial results and registry observations is unclear.[26]

Because systemic and local-regional therapies have changed and the sample size of patients with breast cancer in the NCDB has grown to more than 2,000,000 patients since prior publications, we aimed to update the association between type of surgery and OS in the NCDB.

Primary Model

In our primary adjusted model inclusive of 248,278 matched patients, those patients undergoing lumpectomy compared with those undergoing mastectomy had worse survival (HR 1.02; CI, 1.00-1.04; $P = .002$). This result differs from nearly all prior observational publications.[12-25]

Subgroup Analyses

In stage I-III matched patients, the results differed by ER status. ER+ patients who underwent lumpectomy had worse OS than those who underwent mastectomy. There was no difference in OS by type of surgery in ER− patients.

The association between type of surgery and OS also differed by stage. In models in which matched patients of any ER status were included, those with stage 1 undergoing lumpectomy had worse OS than those who underwent mastectomy. There was no difference if they were stage II. Lumpectomy had better OS than mastectomy if they were stage III.

After matching, then separation by stage and ER status, lumpectomy had better OS than mastectomy in stage III patients and mastectomy had better OS in stage I patients regardless of ER status. Thus paradoxically, in the subgroup analyses, less surgery (lumpectomy) was associated with better survival in patients with a higher stage of cancer and more surgery (mastectomy) was associated with better survival in patients with a lower stage of cancer. This finding was not anticipated and we are unaware of similar findings reported by others with a sample size and study design similar to the present study. On the other hand, some observational studies have identified a few differences in the association between type of surgery and survival when they compared their overall with their subgroup analyses.[13,16,21,22]

In patients with stage III breast cancer, the impact of type of surgery on OS is rarely reported. These patients were excluded from most randomized trials. Consequently, we encourage further exploration regarding the impact of type of surgery on OS by stage. Also, there were some significant differences in OS by type of surgery after patients were stratified by ER status; however, the absolute differences were small, questioning their clinical significance. If these findings are confirmed by future independent analyses in the NCDB and other patient registries, then more personalized discussions of the comparative effectiveness of different types of surgery stratified by stage and hormone receptor status could be considered.

PSM was used in all models here. In observational studies, the presumed advantage of PSM compared with conventional multivariate models is that it controls better for confounding variables.[13,15,25]

Clinical Significance

Given such a large patient sample size in the NCDB, small differences in the absolute values for OS by type of surgery were often statistically significant. To our knowledge (in observational oncologic studies) there is no standard prestudy noninferiority threshold level for the survival HR to define a "clinically significant difference" between exposure variables. In contrast, a priori thresholds for clinical noninferiority are common in randomized trials.[31-33] For example, in the ACOSOG Z0011 trial, an HR of 1.3 or less was established for noninferiority between the study arms of omission versus receipt of axillary dissection after a positive sentinel node biopsy.[31] The methodology to establish a threshold for a noninferior HR between predictor variables is not exact and consensus is difficult to achieve.[34-36] Further, systematic reviews indicate inconsistency of how noninferiority is used.[34] In this context, many of our HRs, including our primary model of all matched patients (HR 1.02), were within ranges that have been used in numerous publications to establish noninferiority between the treatment arms.

In our primary model inclusive of all patients, why does the association of type of surgery with OS differ from most prior observations?

To understand the discrepancies between the results here and others, we compared our study design with the other observational publications.[12-25] Major methodologic differences were identified, including but not limited to criteria for patient inclusion, exclusion, adjustment, and the handling of missing values. To date, there has been a notable lack of uniformity. For example, in multiple analyses, those patients with contralateral prophylactic mastectomy, reconstruction after mastectomy, tumor size $>$ 3 cm, positive nodes, nonductal (but primary breast) histology, or undergoing nipple-sparing mastectomy were excluded.[13-16,19] In other reports, only patients of certain ages or who had their cancer diagnosis made by screening were included. We included all these patient types because they were included in many clinical trials and they reflect our daily practice. In other reports, patients who did not receive radiation after lumpectomy were excluded; surprisingly so because the stated purpose of many observational studies has been to validate trial results.[13,14,16,17,19,20] The NSABP B 06 trial included these patients.[1,2] Also, there was no uniformity of predictor variables among past studies. For example, receipt of radiation, sometimes linked to surgery type or perhaps excluded from the mastectomy cohort, was inconsistently used as either a treatment or adjustment variable along with the other adjuvant therapies (hormone and chemotherapy). Notably absent from many studies were descriptions for how patient encounters were handled when there was no value recorded for an adjustment variable. In a SEER study, these patients were excluded.[14] They were included here. Some researchers have argued that a bias can be introduced if patients with missing values for adjustment variables are excluded because they may be unequally distributed between the study exposures. In other words, missing data may not be missing at random.[37,38]

More controlling variables were used in our modeling compared with other studies. "More" does not mean better; however, each of our confounding variables can be justified by the reason that all have been identified in past studies to be associated with OS. For example, unlike others, we included time from diagnosis to first treatment in our models.[39,40] Moreover, many studies failed to adjust for comorbidities or receipt of adjuvant systemic or radiation treatment. Overall, the difference in the predictor and confounding variables between investigators was striking.[12-25] Besides these design differences, sample sizes ranged from fewer than 10,000 to more than 800,000 in the study here. To our knowledge, our sample size of patients after matching (248,278) exceeded the largest prior unmatched sample size for this study topic.

Limitations

The limitations of the NCDB, and other registries, are well-described elsewhere and apply here too.[13,41,42] For example, some patients are lost to follow-up and study data are observational. Thus, differences in OS by type of surgery could be the result of unmeasured confounders.[12,15] Also, data fields may be misclassified or missing in the NCDB. It is not possible to ascertain how often misclassification occurs. Missing data was addressed in a few studies that we reviewed, but how it was handled analytically varied across studies. Only a single report was found that used imputation to account for missing values.[19] In addition, in the NCDB, other factors associated with OS, such as HER 2 status and tumor multigene signature tests, have been captured only recently, not allowing enough follow-up time to include them as adjustment variables across all years of the current study.

Conclusion

A reappraisal of the association between type of breast cancer surgery and OS was undertaken. In our primary model inclusive of more than 200,000 stage I-III matched patients, we found differences in OS by type of surgery; however, there was no survival disadvantage in those patients undergoing mastectomy compared with those undergoing lumpectomy during a decade when mastectomy rates were rising, and more than a dozen reports concluded that lumpectomy had better OS. We hope these findings can be reassuring to patients and useful for providers during their shared decision-making discussions.

We propose the difference between the observations here compared with past publications is mostly due to dissimilar study designs, especially for the inclusion, exposure, and adjustment variables. As such, standardization of which variables to use when national registries are used to identify predictors of breast cancer survival ought to be considered. Such an effort would build on recent efforts by registry stewards to harmonize analytic methodology and to communicate the extent of registry-specific limitations.[42-46] Future refinements in modeling for breast cancer survival studies will be necessary as new prognostic molecular and multigene signature tests emerge. Thus, study designs would need to be updated as needed and iterative.

Clinical Practice Points

- Past observational studies focusing on the association between type of breast cancer surgery and OS are concerning because they document rising mastectomy rates coinciding with more than a dozen reports that lumpectomy has better OS than mastectomy. These results differ from the randomized trials that launched the lumpectomy era, which demonstrated survival equivalency by type of surgery.
- In a contemporary analysis, 845,136 patients in the NCDB underwent propensity score matching by type of surgery. Compared with and different from older observational reports, we found that stage I-III patients undergoing mastectomy did not have inferior survival to those undergoing lumpectomy.
- Subgroup analyses demonstrated that the association between type of surgery and OS changed by ER status and stage.
- In an era of increasing mastectomies, these data provide reassurance that mastectomy does not have inferior survival compared with lumpectomy.
- Further investigations into the association between type of surgery and OS are indicated as new therapies emerge and to corroborate or refute the associations between type of surgery and OS by stage and ER status identified in the current study.
- Due to the multiplicity of competing study designs and in alignment with multiple oncology registry stewards, we recommend attempts to harmonize the predictor and adjustment variables to be used in future comparative survival analyses that use national databases.

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Disclosure

The authors have states that they have no conflicts of interest.

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