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Research Article

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Patterns of Care and Predictors of Survival among DCIS Patients: An NCDB Analysis

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Abstract

Introduction: The optimal treatment of ductal carcinoma *in situ* (DCIS) remains controversial. The aims of this study were to: 1) Evaluate patterns of treatment and, 2) Identify predictors of survival among patients diagnosed with DCIS.

Methods: The National Cancer Database (NCDB) was queried to identify all patients diagnosed with DCIS between 2004-2015. After applying exclusion criteria, Cox proportional hazards and Kaplan-Meier analysis were performed to compare treatment groups and estimate risk of death stratified by demographics, clinical features, and treatment delivered. An average treatment effect (ATE) was calculated between three matched treatment cohorts of interest: Lumpectomy alone, extended local therapy (lumpectomy/radiation or mastectomy) and extended local therapy + anti-hormonal therapy.

Results: Among 34,444 patients diagnosed with DCIS who met inclusion criteria, the mean age at diagnosis was 60. Patients who received lumpectomy alone were older, and had smaller, and more well-differentiated tumors compared to other treatment cohorts ($p < 0.001$). After calculating ATE among matched cohorts, patients who underwent extended local therapy (HR = 0.81, 95% CI: 0.73-0.90) and extended local therapy + anti-hormonal therapy (HR = 0.61, 95% CI: 0.54-0.68) had improved survival compared to lumpectomy alone ($p < 0.001$). At 120 months, anti-hormonal therapy had a significant impact upon survival for ER/PR positive tumors (HR = 1.45, $p < 0.001$) but not ER/PR negative tumors (HR = 1.15, $p = 0.188$). Additional predictors of reduced survival on MVA included African-American race (HR = 1.37, 95% CI: 1.21-1.55), increased Charlson-Deyo score (HR = 2.82, 95% CI: 2.37-3.36), older age at diagnosis (HR = 6.48 95% CI: 5.31-7.91), and Medicaid insurance (HR = 2.03, 95% CI: 1.64-2.52) (all $p < 0.001$).

Conclusions: Among patients diagnosed with DCIS, extended local therapy plus the addition of anti-hormonal therapy significantly reduced mortality by 2.2% and 3.5% at 60 months among matched cohorts. Although the NCDB does not capture recurrence or breast-cancer specific mortality, these results suggest that additional therapy beyond surgery alone may improve mortality for patients diagnosed with DCIS and warrants further investigation.

Abbreviations

DCIS: Ductal Carcinoma *in Situ*; NCCN: National Comprehensive Cancer Network; RT: Radiation Therapy; NCDB: National Cancer Database; PUF: Participant User Data File; COC: Commission on Cancer; ATE: Average Treatment Effect; CI: Confidence Intervals

Introduction

The treatment of ductal carcinoma *in situ* (DCIS, intraductal carcinoma, stage "0" breast cancer) of the breast is varied and controversial, with overtreatment and under-treatment both causes of concern [1-7]. Reflecting the lack of consensus, national guidelines allow for a wide range of local treatment options [8-11]. Current National Comprehensive Cancer Network (NCCN) guidelines recommend complete local therapy (lumpectomy with radiation) with the addition of anti-hormonal therapy as appropriate, but also consider the omission of radiation therapy (RT) and/or anti-hormonal therapy and use of mastectomy appropriate for certain patient populations. Radiation and anti-hormonal therapy have

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been shown to reduce recurrence without affecting survival, and outcomes of surveillance without surgery are being evaluated by several open randomized clinical trials [12-15]. The aim of this study was to examine patterns of care among patients captured by the National Cancer Database (NCDB) diagnosed with DCIS and to compare clinic opathologic features and overall survival (OS) among varied treatment cohorts. We chose three treatment cohorts of particular interest as follows: 1) Lumpectomy alone, 2) Extended local therapy (lumpectomy + XRT or mastectomy), and 3) Extended local therapy plus anti-hormonal therapy.

Methods

Data source

Our data sample was extracted from the National Cancer Database (NCDB)'s Participant User Data File (PUF) for breast cancer. Created in 1989 by the American College of Surgeons' Commission on Cancer (CoC) and the American Cancer Society, the NCDB is a registry that captures roughly 70% of U.S. cancer cases The NCDB contains approximately 34 million records from CoC accredited cancer registries across the United States. The registry includes demographics, clinic pathologic and treatment data, OS is measured but not recurrence or cancer-specific survival [16]. The NCDB PUF contains de-identified patient and facility data and therefore, is complaint with the Health Insurance Portability and Accountability Act (HIPAA) and exempt from Institutional Review Board review.

Study population

Our study population consisted of all NCDB reported cases of DCIS diagnosed between 2004 and 2015. We included stage 0 breast cancers and first or only cancers. Histologic patterns included were intraductal carcinoma, comedocarcinoma, intraductal papillary adenocarcinoma, and intraductal concomitant with lobular carcinoma, all non-infiltrating. We excluded male patients, invasive and microinvasive tumors, lobular carcinoma *in situ* without associated DCIS, positive nodes, positive margins, missing anti-hormonal receptor statuses, cases where treatment was not performed at the reporting facility, cases without surgical excision of the primary tumor site, all 90-day mortalities, missing outcomes or undetermined treatment patterns. Margin size is not captured by the NCDB. Since our interest was to compare local and systemic therapy groups, patients who had bilateral mastectomy were excluded as this additional surgery was beyond standard, recommended local control. Three treatment cohorts of interest were then defined as follows: 1) Lumpectomy alone, 2) Extended local therapy (lumpectomy with RT or mastectomy), 3) Extended local therapy with anti-hormonal therapy.

Statistical methods

The frequencies of variables of interest among the entire study cohort are listed in (Table 1). Univariate (UVA) and multivariable (MVA) analysis (built by backward variable se-

Table 1: Characteristics of patients diagnosed with DCIS.

Variable		n (%) = 34,444
Treatment Cohort	Lumpectomy Alone	4,768 (13.8)
	Local Therapy	15,446 (44.8)
	Local therapy + Hormone	14,230 (41.3)
Age (quartile)	> = 23, < = 51	9,428 (27.4)
	> 51, < = 59	8,059 (23.4)
	> 59, < = 68	8,894 (25.8)
	> 68, < = 90	8,063 (23.4)
Race	White	28,384 (82.4)
	Black	4,249 (12.3)
	Other/Unknown	1,811 (5.3)
Charlson-Deyo Score	0	29.747 (86.4)
	1	3,975 (12.3)
	2+	722 (2.1)
Facility Type	Community Cancer Program/Other	3,171 (9.4)
	Comprehensive Community Cancer Program	16,961 (50.3)
	Academic/Research Program	9,043 (26.8)
	Integrated Network Cancer Program	4,544 (13.5)
	Missing	725
Primary Payor	Not Insured/Unknown	914 (2.7)
	Private	20.757 (60.3)
	Medicaid/Other Government	1,822 (5.3)
	Medicare	10,951 (31.8)

Year of Dx	> = 2004, < = 2008	11,027 (32.0)
	> 2008, < = 2010	11,320 (32.9)
	> 2010, < = 2012	6,021 (17.5)
	> 2012, < = 2013	6,076 (17.6)
Histology	Ductal	25,358 (73.6)
	Comedocarcinoma	6,130 (17.8)
	Papillary	1,082 (3.1)
	Ductal + lobular	1,874 (5.4)
Hormonal Status	ER/PR +	5,783 (16.8)
	ER/PR -	28,661 (83.2)
HER-2 Status	Negative	2317 (6.7)
	Positive	1258 (3.7)
	Unknown	30,869 (89.6)
Grade	Well Differentiated	3,497 (10.2)
	Moderately Differentiated	9,870 (28.7)
	Poorly Differentiated/Undifferentiated	14,005 (40.7)
	Cell Type Not Determined	7.072 (20.5)
Tumor Size (quartile) (cm)	> = 0.1, < = 0.5	7,144 (20.7)
	> 0.5, < = 1	5,957 (17.3)
	> 1, < = 1.9	5,695 (16.5)
	> 1.9, < = 98.8	6,218 (18.1)
	Unknown	9,430 (27.4)
Hormonal Therapy	No	20,214 (58.7)
	Yes	14,230 (41.3)
Immunotherapy	No	34,293 (99.6)
	Yes	60 (0.2)
	Unknown	91 (0.3)
Radiation	No	11,900 (34.5)
	Yes	22,544 (65.5)

*Local Therapy = Lumpectomy + Radiation.

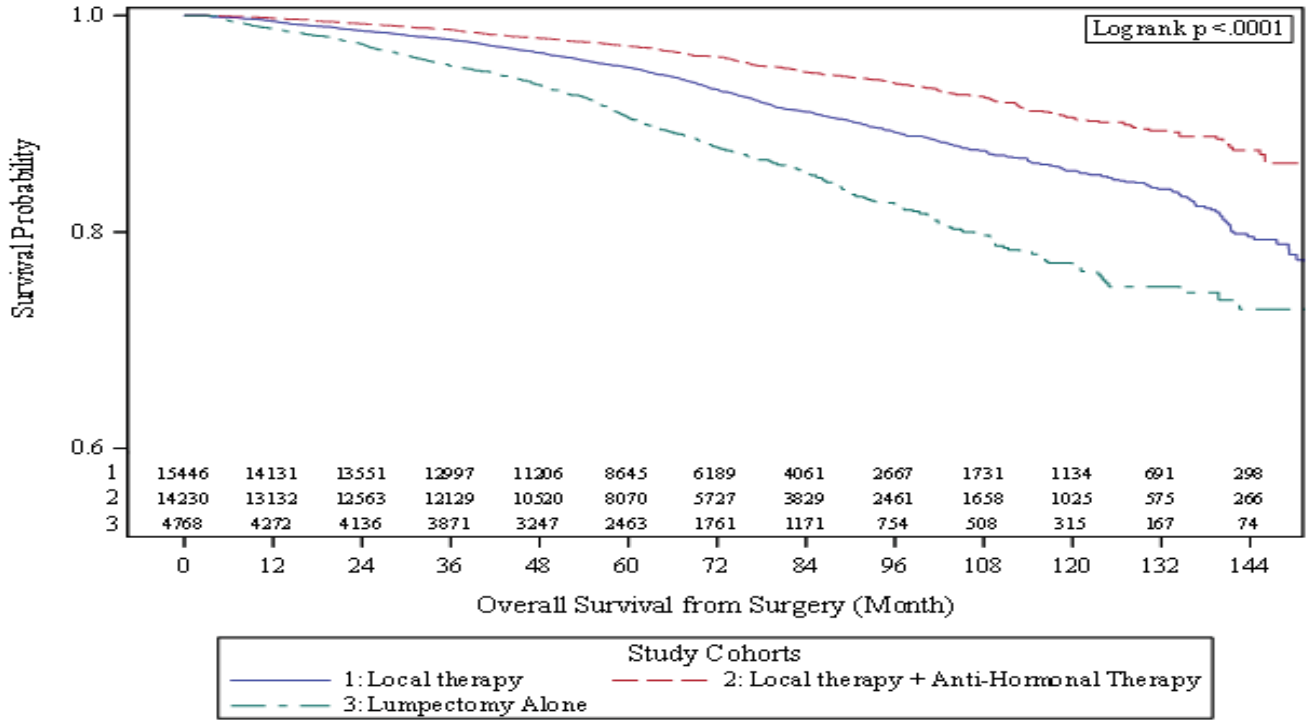
Table 2: Univariate and Multivariate Model for the Association with Overall Survival (OS).

Variable		**UVA HR (95% CI)**	**p-value**	**MVA HR (95% CI)**	**p-value**
Treatment Cohort	Local Therapy	0.57 (0.51-0.63)	< 0.001	0.69 (0.62-0.77)	< 0.001
	Local Therapy + Hormone	0.33 (0.30-0.38)		0.51 (0.45-0.58)	
	Lumpectomy Alone	Ref		Ref	
Age (quartile)	> 68, < = 90	11.64 (9.89-13.70)	< 0.001	6.48 (5.31-7.91)	< 0.001
	> 59, < = 68	3.28 (2.74-3.93)		2.49 (2.05-3.01)	
	> 51, < = 59	1.77 (1.45-2.17)		1.67 (1.36-2.05)	
	> = 23, < = 51	Ref		Ref	
Race	Black	1.31 (1.16-1.48)	< 0.001	1.37 (1.21-1.55)	< 0.001
	Other/Unknown	0.51 (0.40-0.67)		0.67 (0.52-0.88)	
	White	Ref		Ref	

Charlson-Deyo Score	2+	4.58 (3.85-5.45)	< 0.001	2.82 (2.37-3.36)	< 0.001
	1	1.93 (1.72-2.16)		1.42 (1.27-1.59)	
	0	Ref		Ref	
Facility Type	Community Cancer Program/Other	1.32 (1.13-1.53)	0.006	1.21 (1.04-1.41)	0.107
	Comprehensive Community Cancer Program	1.09 (0.98-1.20)		1.03 (0.93-1.15)	
	Integrated Network Cancer Program	1.06 (0.92-1.23)		1.04 (0.90-1.21)	
	Academic/Research Program	Ref		Ref	
Primary Payor	Not Insured/Unknown	2.48 (1.89-3.26)	< 0.001	1.87 (1.42-2.48)	< 0.001
	Medicaid/Other Government	2.35 (1.91-2.91)		2.03 (1.64-2.52)	
	Medicare	5.42 (4.92-5.97)		1.74 (1.53-1.98)	
	Private	Ref		Ref	
Year of Diagnosis	> = 2004, < = 2008	0.93 (0.78-1.11)	0.204	NS	
	> 2008, < = 2010	1.04 (0.87-1.24)			
	> 2010, < = 2012	0.96 (0.78-1.18)			
	> 2012, < = 2013	Ref			
Histology	Comedocarcinoma	1.04 (0.93-1.16)	< 0.001	NS	
	Papillary	1.56 (1.27-1.90)			
	Ductal + lobular	0.81 (0.66-1.00)			
	Ductal	Ref			
ERPR	ERPR+	0.76 (0.69-0.85)	< 0.001	0.95 (0.85-1.05)	0.348
	ERPR -	Ref		Ref	
HER2	Negative	1.08 (0.78-1.48)	0.582	NS	
	Unknown	0.97 (0.75-1.27)			
	Positive	Ref			
Grade	Moderately Differentiated	1.0 (0.87-1.17)	0.765	NS	
	Poorly Differentiated/Undifferentiated	0.96 (0.83-1.10)			
	Cell Type Not Determined	1.00 (0.85-1.17)			
	Well differentiated	Ref			
Tumor Size Quartile (cm)	> 0.5, < 1		0.002	1.25 (1.09-1.44)	0.004
	> 1, < = 2	1.28 (1.12-1.47)		1.17 (1.02-1.36)	
	> 2, < = 99	1.19 (1.03-1.37)		1.27 (1.10-1.46)	
	Unknown	1.26 (1.10-1.45)		1.11 (0.98-1.26)	
	> 0.1, < 0.5	Ref		Ref	

*NS: Not selected by the backward variable elimination, and not significant at p < 0.2.

lection with alpha = 0.2 removal criteria) were performed to determine associations between variables of interest and OS using a Cox proportional hazard model (yielding hazard ratios [HR] with 95% confidence intervals [CI]) as reported in (Table 2). Ten-year OS using Kaplan Meier analysis was conducted for treatment cohorts of interest (with log rank test performed to determine p values) (Figure 1). Associations between variables of interest and these three treatment groups were examined using chi-square for categorical variables and ANOVA for continuous covariates (Table 3). To further reduce the selection bias, the inverse probability treatment weighting method, a propensity score based approach was also implemented to balance patient's baseline characteristics. A multinomial logistic regression model was carried out to estimate the probabilities that a patient would receive either lumpectomy, extended local therapy, or extended local therapy + anti-hormonal therapy based on their baseline covariates that also predict overall survival. The balance of covariate between cohorts was evaluated by the standardized differences and a value of < 0.1 was considered as negligible imbalance [17]. The average treatment effect (ATE) by the three cohorts associated with OS was estimated in a weighted Cox proportional hazard model. The subgroup analyses were carried out in the multivariable model with interaction between treatment groups and ER/PR status. The analyses were done in SAS 9.4 and Winship BBISR SAS macros, and significance level was set at alpha < 0.05 [18].



Study Cohorts	No. of Subject	Event	Censored	Median Survival (95% CI)	60 Mo Survival	120 Mo Survival
Local therapy	15446	1070 (7%)	14376 (93%)	NA (NA, NA)	95.2% (94.8%, 95.6%)	85.7% (84.6%, 86.7%)
Local therapy + Anti-Hormonal Therapy	14230	582 (4%)	13648 (96%)	NA (NA, NA)	97.2% (96.8%, 97.5%)	90.5% (89.4%, 91.5%)
Lumpectomy Alone	4768	546 (11%)	4222 (89%)	NA (158.9, NA)	90.5% (89.5%, 91.4%)	76.9% (74.4%, 79.1%)

Figure 1: Overall Survival all patients diagnosed with DCIS stratified by treatment group.

Table 3: Association between variables of interest and three treatment groups.

Variable		Lumpectomy Alone n = 4768	Local Therapy n = 15446	Systemic Therapy n = 14230	p-value
Age at diagnosis	Mean	63.7	60.03	57.8	< 0.001
	Median	64	60	58	
	Std Dev	13.25	11.77	10.35	
Age (quartile)	> = 23, < = 51	1003 (21.04)	4083 (26.43)	4342 (30.51)	< 0.001
	> 51 < = 59	880 (18.46)	3456 (22.37)	3723 (26.16)	
	> 59, < = 68	1045 (21.92)	3986 (25.81)	3863 (27.15)	
	> 68, < = 90	1840 (38.59)	3921 (25.39)	2302 (16.18)	
Race	White	3930 (82.42)	12852 (83.21)	11602 (81.53)	0.002
	Black	576 (12.08)	1804 (11.68)	1869 (13.13)	
	Other/Unknown	262 (5.49)	790 (5.11)	759 (5.33)	
Carlson-Deyo Score	0	4132 (86.66)	13197 (85.44)	12418 (87.27)	< 0.001
	1	523 (10.97)	1901 (12.31)	1551 (10.9)	
	2+	113 (2.37)	348 (2.25)	261 (1.83)	

Facility Type	Commun. Cancer Program/ Other	431 (9.22)	1234 (8.2)	1506 (10.77)	< 0.001
	Comp Commun Cancer Program	2396 (51.24)	7559 (50.21)	7006 (50.08)	
	Academic/Research Program	1228 (51.24)	4216 (28.01)	3599 (25.73)	
	Integrated Network Cancer Program	621 (13.28)	2045 (13.58)	1878 (13.42)	
Primary Payor	Not Insured/Unknown	141 (2.96)	392 (2.54)	381 (2.68)	<0.001
	Private	2367 (49.64)	9087 (58.83)	9303 (65.38)	
	Medicaid/Other Government	208 (4.36)	739 (4.91)	855 (6.01)	
	Medicare	2052 (43.04)	5208 (33.72)	3691 (25.94)	
Year of Diagnosis	> = 2004, < = 2008	1603 (33.62)	5078 (32.88)	4346 (30.54)	< 0.001
	> 2008, < = 2010	1508 (31.63)	5199 (33.66)	4613 (32.42)	
	> 2010, < = 2012	813 (17.05)	2609 (16.89)	2599 (18.26)	
	> 2012, < = 2013	844 (17.7)	2560 (16.57)	2672 (18.78)	
Histology	Ductal	3696 (77.52)	11163 (72.27)	10499 (73.78)	< 0.001
	Comedocarcinoma	593 (12.44)	3108 (20.12)	2429 (17.07)	
	Papillary	238 (4.99)	390 (2.52)	454 (3.19)	
	Ductal + lobular	241 (5.05)	785 (5.08)	848 (5.96)	
Hormonal Receptor Status	ER/PR -	723 (15.16)	4,648 (30.09)	412 (2.9)	< 0.001
	ER/PR +	4,045 (84.84)	10,798 (69.91)	13,818 (97.1)	
HER2	Negative	302 (6.33)	882 (5.71)	1,113 (7.96)	< 0.001
	Positive	113 (2.73)	670 (4.34)	475 (3.34)	
	Unknown	4,353 (91.3)	13,894 (89.95)	12,622 (88.7)	
Grade	Well Differentiated	776 (16.28)	1202 (7.78)	1519 (10.67)	< 0.001
	Moderately Differentiated	1505 (31.56)	3866 (25.03)	4499 (31.62)	
	Poorly Differentiated	1395 (29.26)	7247 (46.92)	5363 (37.69)	
	Cell Type Not Determined	1092 (22.9)	3131 (20.27)	2849 (20.02)	
Tumor Size (cm)	Mean	1.34	1.79	1.42	< 0.001
	Median	0.8	1.2	1	
	Std. Dev	3.48	2.89	2.32	
Tumor Size (quartile) (cm)	> = 0.1, < = 0.5	1257 (26.36)	2790 (18.06)	3097 (21.76)	< 0.001
	> 0.5, < = 1	820 (17.2)	2537 (16.42)	2600 (18.27)	
	> 1, < = 1.9	660 (13.84)	2724 (17.64)	2311 (16.24)	
	> 1.9, < = 9.8	650 (13.63)	3323 (2.51)	2245 (15.78)	
	Unknown	1381 (28.96)	4072 (26.36)	397 (27.95)	

Results

Study population, demographics, clinicopathologic and treatment variables

The NCDB breast PUF (2004-2014) identified a total of 2,696,734 breast cancer cases. After applying the inclusion and exclusion criteria listed in (Table 4), a total of 34,444 patients met selection criteria with a median follow-up 63.9 months. Descriptive characteristics of this population regarding variables of interest are listed in (Table 1). The mean age of diagnosis was 59-years (std. dev. 12), the majority of patients were Caucasian (82.4%), treated at a comprehensive community cancer program (50.3%) and had private insurance (60.3%). The treatment cohorts of interest are listed in (Table 1). The majority received additional treatment beyond lumpectomy: 4,768 (13.8%) received lumpectomy alone 15,446 (44.8%) received either lumpectomy with radiation or unilateral mastectomy 14,230 (41.3%) received extended local therapy with additional anti-hormonal therapy.

Univariate, multivariate and Kaplan Meier analysis of variables associated with decreased overall survival and Kaplan Meier 10-year overall survival

The results of univariate (UVA) and multivariate (MVA)

Table 4: Inclusion and exclusion criteria.

Selection and Exclusion Criteria	Sample Size	Excluded
NCDB Breast PUF Cancer Cases	2696734	-
Year of diagnosis 2004 ~ 2015	1982168	714566
Include sequence number in 0 or 1	1645418	336750
Exclude cases treatment decision was not done at reporting facility	1581834	63584
Include Histology 8500 8501 8503 8522	1176472	405362
Exclude male patients	1165374	11098
Exclude tumor behavior as invasive	157044	1008330
Include Clinical and Pathological stage 0	57329	99715
Include Diagnostic Confirmation as 1 2	57320	9
Exclude Tumor Invasive Component defined by CS_SITESPECIFIC_FACTOR_6	57297	23
Exclude cases with positive regional nodes	57297	0
Exclude cases without surgery at primary site or unknown	56988	309
Include Surgical Margin as negative	54611	2377
Exclude cases died within 90 day after surgery	54558	53
Exclude missing outcome	53909	649
Include ERPR as 0 1	46641	7268
Exclude cases with bilateral mastectomy	34444	12197

*Sequence number: 0 = only cancer, 1 = first cancer.

*Histology: 8500 = DCIS, 8501 = comedocarcinoma, non infiltrating, 8503 = intraductal papillary adenocarcinoma, non infiltrating, 8522 = DCIS + LCIS.

*CS_SITESPECIFIC_FACTOR_6 = Invasive Component.

Table 5: Multivariable model for OS in weighted overall samples and weighted subpopulation.

Covariate	Level	Hazard Ration (95% CI)	HR p-value
Overall	Local therapy	0.81 (0.73-0.90)	< 0.001
	Local therapy + Hormone	0.61 (0.54-0.68)	< 0.001
	Lumpectomy Alone	Ref	
Subgroup*: ER/PR+	Local therapy vs. Lumpectomy Alone	0.88 (0.77-1.00)	0.046
	Local therapy + Hormone vs. Lumpectomy Alone	0.60 (0.53-0.69)	< 0.001
	Local therapy vs. Local therapy + Hormone	1.45 (1.30-1.62)	< 0.001
Subgroup*: ER/PR-	Local therapy vs. Lumpectomy Alone	0.61 (0.48-0.78)	< 0.001
	Local therapy + Hormone vs. Lumpectomy Alone	0.53 (0.41-0.68)	< 0.001
	Local therapy vs. Local therapy + Hormone	1.15 (0.93-1.42)	0.188

*The treatment comparison in the subgroups was estimated by the multivariable model with interaction, and the interaction p-value is 0.023.

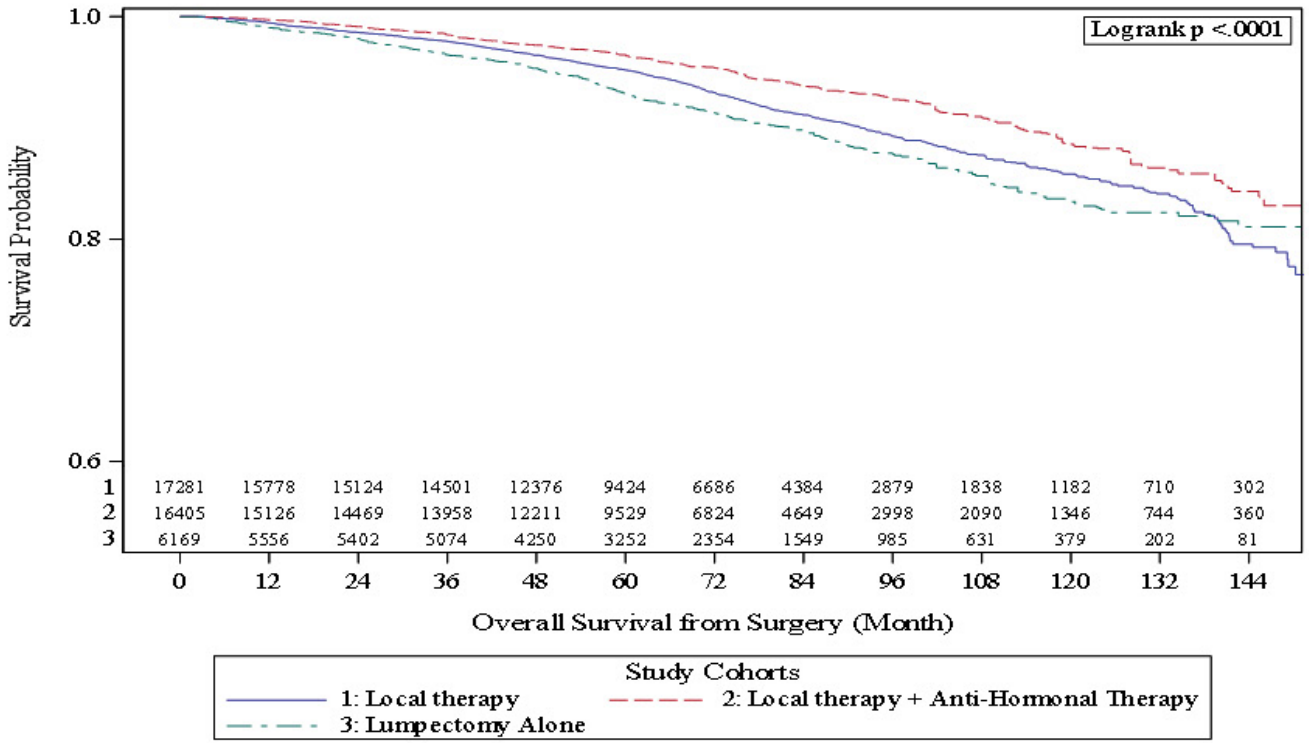
analysis of the association between variables of interest and OS are listed in (Table 2). Factors associated with decreased survival on univariate analysis included lumpectomy treatment alone, African-American race (HR = 1.31, 95% CI: 1.16-1.48, p < 0.001), increased age (HR = 11.64, 95% CI 9.89-13.70, p < 0.001), increased Charlson-Deyo score (HR = 4.58, 95% CI: 3.85-5.45, p < 0.001), any insurance other than private especially Medicare (HR = 5.42, 95% CI: 4.92-5.97, p < 0.001), papillary histology (HR = 1.56, 95% CI: 1.27-1.90, p < 0.001), ER/PR negative receptor status (HR = 0.76, 95% CI: 0.69-0.85, p < 0.001), and larger tumor size (HR = 1.26, 95% CI: 1.10-1.45, p < 0.002). On MVA, lumpectomy alone, increased age (HR = 6.48, 95% CI: 5.31-7.91, p < 0.001), African-American race (HR = 1.37, 95% CI: 1.21-1.55, p < 0.001), increased Charlson-Deyo score (HR = 2.82, 95% CI: 2.37-3.36, p < 0.001), any insurance other than private especially Medicaid (HR = 2.03, 95% CI: 1.64-2.52, p < 0.001), and increased tumor size (HR = 1.27, 95% CI: 1.10-1.26, p < 0.004) were associated with decreased survival. Kaplan-Meier analysis was performed to determine ten-year OS and stratified by treatment cohorts of interest as shown in Figure 1. Lumpectomy alone had a decreased 10-year survival (76.9%, 95% CI: 74.4-79.1%) compared to extended local therapy (85.7%, 95% CI: 84.6-86.7%) and extended local therapy with anti-hormonal therapy (90.5%, 95% CI: 89.4-91.5%) (p < 0.001).

By utilizing inverse probability treatment weighting, a satisfactory covariate balance was achieved for the overall population as well as in the subgroups by ER/PR status. Multivariable analysis was performed among this weighted sample. Extended local therapy with anti-hormonal therapy still provided a survival advantage over other treatment cohorts (HR = 0.61, 95% CI: 0.54-0.68). Anti-hormonal therapy had a significant impact upon survival for ER/PR positive tumors (HR = 1.45, p < 0.001) but not ER/PR negative tumors (HR = 1.15, p = 0.188) (Table 5). Kaplan Meier analysis confirmed this survival advantage among these weighted cohorts with lumpectomy alone having 83.4% (95% CI: 80.7-85.7%) 10-year survival compared to 85.8% (95% CI: 84.7-86.9%) for extended local therapy and 88.5% (95% CI: 86.5-90.0%) for extended local plus anti-hormonal therapy (p < 0.001) (Figure 2).

Discussion

Patients diagnosed with DCIS have an excellent prognosis with an estimated 20-year disease-specific mortality of 3% [12,13]. Given the excellent prognosis of DCIS, the optimal treatment to reduce mortality without added toxicity of additional treatment is controversial. Among this cohort of DCIS patients, additional local therapy beyond breast conserving surgery (BCS) alone with either radiation or unilateral mastectomy and the further addition of anti-hormonal therapy reduced mortality by 2.2% and 3.5% at 60 months and by 2.4% and 5.1% at 120 months, among matched cohorts respectively (see (Figure 2)).

Characteristics and treatment patterns of patients diagnosed with DCIS are shown in (Table 1), the demographics



Study Cohorts	No. of Subject	Event	Censored	Median Survival (95% CI)	60 Mo Survival	120 Mo Survival
Local therapy	15054	1063 (7%)	13991 (93%)	NA (NA, NA)	95.2% (94.8%, 95.6%)	85.8% (84.7%, 86.9%)
Local therapy + Anti-Hormonal Therapy	13989	580 (4%)	13409 (96%)	NA (NA, NA)	96.5% (96.0%, 96.9%)	88.5% (86.9%, 90.0%)
Lumpectomy Alone	4676	544 (12%)	4132 (88%)	NA (158.9, NA)	93.0% (92.0%, 93.9%)	83.4% (80.7%, 85.7%)

Study Cohorts	Overall Survival from Surgery (Month)	Survival Rate (95% CI)
Local therapy	120	85.8% (84.6%, 86.9%)
Local therapy + Hormone	120	88.3% (86.5%, 89.9%)
Lumpectomy Alone	120	83.3% (80.7%, 85.6%)

Figure 2: KM Overall Survival ATE SW.

of our cohort are similar to other national studies [12]. Our results are similar to a recent SEER analysis: 14% of patients received lumpectomy alone, 44% received additional local therapy-65% of whom received radiation and 35% of whom received unilateral mastectomy and 41% of patients received adjuvant anti-hormonal therapy. On multivariate analysis, demographic variables associated with decreased survival in our study included those previously reported in the literature including African-American race, increased Charlson-Deyo score, and Medicaid insurance [19-21]. Older patients had a decreased survival. Although younger patients have previously been shown to have decreased breast-cancer survival, in this cohort, older patients had decreased survival likely due to the NCDB's inability to differentiate overall and breast-cancer survival [12,22,23]. Tumor size (> 2 cm) was associated with decreased survival on MVA. Positive margins were entirely excluded, margin size is not included in the NCDB. Tumor grade and histology and receptor status were not associated with survival on MVA. Although studies have attempted to define "low-risk" DCIS as low-intermediate grade, < 2.5 cm tumors with negative margins (> 1 cm) which may be appropriate for less aggressive treatment, our results reflected the findings of ECOG-ACRIN E5194 that determined grade was nota useful marker for predicting risk of recurrence [22,24]. Our results demonstrate that papillary histology was associated with decreased survival on UVA but not MVA. In contrast, the SEER analysis of 108,196 patients performed by Narod etaldemon strated poor prognosis of comedocarcinoma histology [12]. Comedonecrosis is often associated with higher-grade tumors, which were not significantly associated with decreased survival in our study; in contrast, papillary histology has been shown to be more likely associated with invasive cancers and perhaps could represent missed invasive cancers among this cohort and a limitation of this and other NCDB studies. More recent efforts have examined the role of molecular markers in predicting the risk of recurrence after surgical excision [25-30]. ER/PR negative tumors were associated with decreased survival on UVA but not MVA among our cohort. Such tumors have been shown to be associated with decreased survival likely because they do not benefit from the addition of anti-hormonal therapy, although the use of anti-hormonal treatment has been inconsistent as demonstrated in this cohort 83% of patients were hormonal receptor positive but only 41% of anti-hormonal positive patients received anti-hormonal therapy [12]. Although not routinely reported, HER2 did not demonstrate an association with survival among our cohort, the clinical implications of HER2 among DCIS patients is in need of additional study [31].

Both univariate and multivariate analyses of our cohort demonstrated additional treatment beyond lumpectomy alone to be protective and additive. These results were confirmed on Kaplan-Meier analysis stratified by treatment type. Lumpectomy alone had the poorest OS (76.9%) compared to additional local therapy (85.7%) and additional local therapy plus anti-hormonal therapy (90.5%) ($p < 0.001$) (Figure 1). There is a multitude of conflicting evidence regarding the survival benefit of additional treatment beyond lumpectomy alone for DCIS such as radiation, mastectomy and/or anti-hormonal therapy. Randomized trials have demonstrated reduced local recurrence among DCIS patients who receive these additional therapies but lack sufficient power to demonstrate a survival benefit [24,32-39]. Recent population-based studies have demonstrated conflicting results with some suggesting a survival benefit of radiotherapy among a certain subset of "high-risk" patients [13,14]. A recent SEER analysis by Narod of 108,196 patients and a subset analysis of 2947 patients performed by Giannakeas, et al. found that radiotherapy reduced recurrence without decreasing mortality, however, their analysis also demonstrated a subset of patients diagnosed with DCIS who subsequently died of invasive breast cancer without evidence of prior local recurrence, and therefore concluded DCIS has the potential for invasive and even systemic behavior and warrants consideration of systemic therapy to improve survival. The Narod and Giannakeas SEER analyses did not evaluate the impact of anti-hormonal therapy upon recurrence or survival among DCIS patients [13]. A 2018 prospective study of 9,938 women treated in the UK demonstrated a reduction in recurrence but not mortality among patients who used radiation and anti-hormonal therapy [40]. Given our cohort (34,444 patients) is much larger, and one of the larger cohort studies to report the effects of anti-hormonal therapy upon survival for DCIS, our study may have adeqeuate power to capture the small but potentially significant benefits of anti-hormonal therpay upon survival for patients diagnosed with DCIS.

Given the spectrum of treatment options available for the treatment of DCIS, three treatment groups of greatest interest were chosen for additional analysis and matching: Lumpectomy alone, extended local therapy (lumpectomy + XRT or mastectomy) and extended local therapy + anti-hormonal therapy. These three groups were chosen in order to re-examine in particular the mortality benefit of systemic therapy for DCIS patients. Associations between prognostic variables of interest and these three treatment groups were analyzed, as shown in (Table 3). Patients who received lumpectomy alone were older (mean age 63), more likely to have Medicare and have tumors with ductal or papillary histology, well-differentiated and smaller (mean tumor size 1.34 cm).

Given the differences between these three treatment groups, a survival analysis was performed among cohorts via average treatment effect weighting (ATE). After matching cohorts, patients who received lumpectomy alone had a poorer survival (83.3%) compared to the addition of extended local therapy (85.8%) and anti-hormonal therapy (88.3%) after 120 months ($p < 0.001$) (Figure 2). Furthermore, on Cox regression analysis, additional local therapy beyond lumpectomy alone was protective and the addition of anti-hormonal therapy added additional survival benefit to extended local therapy (Table 5). The survival benefit of anti-hormonal therapy was limited to patients with hormone receptor positive tumors suggesting that despite NCDB being unable to capture disease specific mortality, anti-hormonal therapy was potentially impacting survival among this cohort. Our results suggest that additional therapy to surgical excision of DCIS, both radiation and anti-hormonal, be considered to reduce both recurrence and mortality for patients diagnosed with DCIS.

Given the overall excellent survival of DCIS, prior studies

have attempted to identify a subset of patients with an increased risk of mortality from breast cancer that may particularly benefit from additional therapy. Certain clinicopathologic factorsuch as higher nuclear grade, younger age, larger tumor size have been shown to be associated with reduced survival and prognostic scoring model shave been proposed to delineate which patients may safely be omitted from radiotherapy [23]. The survival benefit of additional therapy among our ATE-weighted cohorts questions such conclusions and practices and warrants additional investigation as current prospective studies have failed to clearly identify a subset of patients who can safely omit radiotherapy and/or anti-hormonal therapy following lumpectomy [14,24,41,42].

Our study is retrospective as thus unable to determine causality for the associations we have observed. The NCDB, like other cancer registries, does not capture recurrence or disease-specific mortality, and therefore, we are unable to assess the true breast-cancer specific mortality among this cohort, however, it is the largest registry available for study of a disease that requires ample power for mortality analysis. We have attempted to utilize ATE-weighting to minimize bias and assess mortality differences between matched treatment cohorts. Given the NCDB's large national data source, our results are generalizable to patients across the US. Further investigation is warranted to confirm the effects of additional therapies upon mortality for DCIS, and to attempt to identify subsets of patients who may benefit or may safely be omitted from additional therapy for DCIS.

Conclusion

Among patients diagnosed with DCIS cases diagnosed between 2004-2015, lumpectomy alone (14%) was the sole treatment for one in seven cases. However, using ATE-weighted methodology to compare outcomes of patients diagnosed with DCIS, we observed significantly better overall survival was observed with the addition of extended local therapy (HR = 0.81, 95% CI: 0.73-0.90) and anti-hormonal therapy (HR = 0.61, 95% CI: 0.54-0.68) compared to those who had lumpectomy alone ($p < 0.001$). Although the NCDB does not capture recurrence or breast-cancer specific mortality, these results suggest that additional therapy beyond surgery alone may improve survival for patients diagnosed with DCIS. Further investigation is indicated to elucidate the mechanisms of DCIS invasion and to identify the subset of patients for whom additional therapy may be beneficial or safely omitted.

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