Full Length Article

Prognostic Impact of Radiation Therapy in Pure Mucinous Breast Carcinoma

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Abstract

The National Cancer Database was used to determine the prognostic impact of radiotherapy after breast conserving surgery for patients with pure mucinous breast carcinoma. Adjuvant radiotherapy is associated with a survival advantage for patients with pure mucinous breast carcinoma. Therefore, omission of radiotherapy following breast conserving surgery for this histology is not warranted.

Purpose: Pure Mucinous breast carcinoma (PMBC) is an invasive breast cancer with favorable prognosis. While pathology-specific guidelines exist for PMBC regarding adjuvant chemotherapy and endocrine therapy, no recommendations exist regarding locoregional treatment based on tumor histology. Prognostic impact of radiotherapy for patients with PMBC remains unclear. **Materials and Methods:** The National Cancer Database was queried (2004-2017) for patients with pN0M0 PMBC who underwent lumpectomy. Chi-square testing compared categorical frequencies between patients who received radiotherapy versus those who did not. Propensity score matching created a 1:1 matched cohort of patients who received radiotherapy and patients who didn't. Kaplan-Meier analysis evaluated overall survival (OS). Cox proportional hazard analyses identified clinical and treatment factors prognostic for OS. **Results:** 17,259 patients met selection criteria; 11,087 (74%) received radiotherapy while 3852 (26%) did not. After PSM, radiotherapy (HR 0.629; 95% CI 0.531-0.746), endocrine therapy (HR 0.676; 95% CI 0.567-0.805), black race (HR 0.703; 95% CI 0.498-0.991), and private insurance (HR 0.184; 95% CI 0.078-0.432) were favorable prognostic factors on multivariate Cox regression analysis while age $\geq$ 70 years (HR 2.668; 95% CI 1.903-3.740), tumor size $>$ 20 mm (HR 1.964; 95% CI 1.613-2.391), and CDCC score $>$ 0 (HR 1.770; 95% CI 1.474-2.126) were unfavorable prognostic factors. After PSM, 5-year OS was 86% for those who received radiotherapy and 81% for those who did not ($P < .001$). **Conclusion:** This is the largest study to date on PMBC and the prognostic impact of adjuvant radiotherapy. Radiotherapy is associated with a survival advantage, suggesting omission of radiotherapy is not warranted.

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Introduction

Pure mucinous breast carcinoma (PMBC) is a histologic subtype of invasive breast carcinoma accounting for 1% to 2% of all cases of invasive breast cancer.[1] PMBC is defined as an invasive carcinoma having greater than 90% mucinous component, ie, groups of neoplastic epithelial cells floating in pools of abundant extracellular mucin.[2] PMBC is almost always well or moderately differentiated.[3] PMBC is almost always positive for estrogen receptors (ER-positive), usually positive for progesterone receptors (PR-positive), and usually negative for HER2 overexpression (HER2-negative).[3-4] PMBC is associated with a more favorable clinical outcome with lower rates of lymph node metastases, lower rates of recurrence, and excellent overall survival.[5-7]

Current National Comprehensive Cancer Network (NCCN) guidelines state that breast-conserving therapy is an option for locoregional treatment of invasive breast cancer.[8] Specific systemic therapy recommendations exist for favorable histologies such as mucinous carcinomas, including adjuvant endocrine therapy (ET) for tumors $\geq$ 3 cm and node-positive patients. Adjuvant chemotherapy can also be considered for node-positive patients but is not

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considered necessary.[8] While radiotherapy (RT) is currently recommended as part of breast-conserving therapy (BCT) for invasive breast cancers, there are no specific recommendations regarding locoregional treatment based on breast cancer tumor histology.

Diab et al. questioned the role of adjuvant therapies including radiotherapy for PMBC by showing that overall survival (OS) of patients with mucinous carcinoma and tubular carcinoma of the breast is comparable to that of the general population.[7] Following this publication, practice patterns changed, and these tumors began to be managed less aggressively.[9] To address this, Stauber et al. recently conducted a large retrospective analysis showing that patients with tubular carcinoma of the breast do benefit from radiotherapy following BCS.[10] However, the body of evidence investigating the prognostic impact of radiotherapy as a component of BCT for mucinous carcinoma remains limited. The purpose of this study was to utilize data from the National Cancer Database (NCDB) to determine the prognostic impact of radiotherapy as a component of BCS in patients with mucinous carcinoma, as well as to identify prognostic demographic and clinicopathologic factors for OS in patients with mucinous carcinoma.

Methods and Materials

Data Source and Study Populations

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACoS) and the American Cancer Society. The NCDB collects data from more than 1500 hospitals with ACoS-accredited cancer programs, accounting for 70% of all newly diagnosed cancers in the United States.[11-12] It includes data on tumor characteristics, patient demographics, and survival. The NCDB is not population-based and thus greatly underrepresents rural areas and minority populations.[13] All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The data used in the study were derived from a de-identified Participant User File (PUF).[14] It is therefore exempt from institutional review board oversight.

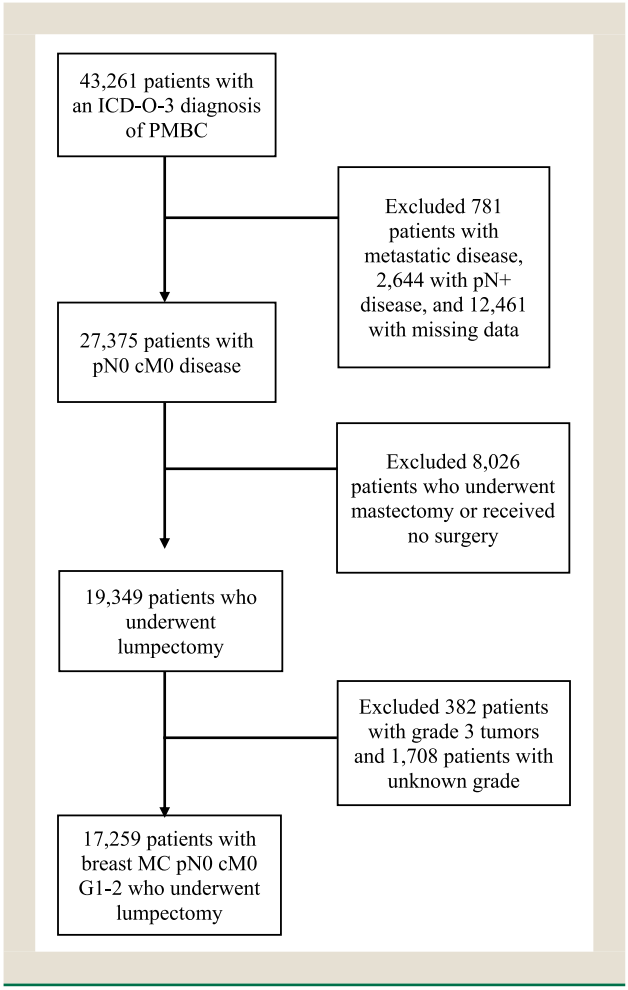
Patient Selection

The NCDB was queried for all patients with a histologically confirmed diagnosis of mucinous carcinoma of the breast (code 8480 from the International Classification of Diseases for Oncology, third edition or ICD-O-3). Patients with nodal or distant metastatic disease at time of diagnosis were excluded from this analysis. Patients who underwent mastectomy or received no surgery at all were also excluded. Because PMBC is almost always well or moderately differentiated, grade 3 tumors were presumed to be erroneously coded as such and were therefore excluded.[3] A flow chart demonstrating selection of the primary study population can be seen in Figure 1.

Statistical Procedures

Pearson Chi-square testing was used to compare categorical frequencies between patients who received radiotherapy versus those who did not. Multivariable binary logistic regression was used to determine indicators that were independently associated with receipt of radiotherapy. Propensity score matching (PSM) was conducted to create a 1:1 matched cohort of patients who received radiotherapy and patients who did not. Univariable (UVA) Cox proportional hazard analyses were used to identify clinical and treatment factors prognostic for OS. Factors prognostic on UVA were included on multivariable (MVA) Cox proportional hazard analyses. Kaplan-Meier log-rank analysis was used to evaluate OS. Statistical analyses were conducted using IBM SPSS Statistics 25 (IBM Inc., Armonk, NY).

Figure 1 Sample selection.



Results

A total of 17,259 patients met selection criteria. Median age was 69 (IQR 60-76). Median tumor size was 13 mm (IQR 8-18), 94.6% of tumors were $\leq$ 3 cm, and the largest tumor size was 17 cm. Of patients for whom exact biomarker data were available, 92% of patients had ER+/PR+/HER2- tumors and 4% of patients had ER+/PR-/HER2- tumors. 11,087 (74%) patients received radiotherapy while 3852 (26%) did not. Radiation doses ranged from hypo fractionated courses of 40.05 Gy in 15 fractions to 50 Gy in 25 fractions. The tumor bed was further boosted in 56.5% of patients. Median follow-up was 64 months.

Overall, 9047 (62%) patients received both RT and ET, 1798 (12%) received only RT, 2045 (14%) received only ET, and 1635

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Table 1 Demographic and Clinicopathologic Details of the Primary Study Cohort, Before PSM.

Demographic Details, n (%)	Overall	RT	NO RT	*P*-value
Age				< .001
< 70	9091 (53)	6981 (63)	863 (22)	
≥ 70	8168 (47)	4106 (37)	2989 (78)	
Sex				.568
Male	47 (0)	31 (0)	13 (0)	
Female	17,212 (100)	11,056 (100)	3839 (100)	
Race				.003
White	14,436 (84)	9209 (84)	3238 (86)	
Black	1822 (11)	1,190 (11)	464 (12)	
Other	855 (5)	595 (5)	62 (2)	
Insurance				< .001
Uninsured	189 (1)	130 (1)	30 (1)	
Private	6322 (37)	4701 (43)	773 (20)	
Medicaid	661 (4)	472 (4)	100 (3)	
Medicare	9734 (57)	5559 (51)	2875 (76)	
Other	160 (1)	111 (1)	23 (1)	
Clinicopathologic Details, n (%)	Overall	RT	NO RT	*P*-value
Laterality				.025
Right	8519 (49)	5541 (50)	1844 (48)	
Left	8730 (51)	5542 (50)	2006 (52)	
Tumor size				.548
≤ 2cm	11,373 (81)	7,353 (81)	2427 (81)	
> 2cm	2636 (19)	1,774 (19)	567 (19)	
ER				.987
ER+	16,838 (99)	10,877 (99)	3,706 (99)	
ER-	162 (1)	106 (1)	36 (1)	
PR				.424
PR+	15,725 (93)	10,148 (93)	3477 (93)	
PR-	1218 (7)	793 (7)	256 (7)	
HER2				< .001
HER2+	390 (3)	271 (4)	53 (2)	
HER2-	11,752 (97)	7462 (97)	2702 (98)	
LVI				.417
LVI present	239 (2)	157 (2)	49 (2)	
LVI not present	10,734 (98)	6828 (98)	2437 (98)	
Radiotherapy				
Yes	11,087 (74)			
No	3852 (26)			
Endocrine Therapy				< .001
Yes	12,774 (77)	9047 (83)	2,045 (56)	
No	3923 (24)	1798 (17)	1,635 (44)	
Chemotherapy				< .001
Yes	1124 (7)	872 (8)	99 (3)	
No	15,770 (94)	10,047 (92)	3,638 (97)	
Charlson-Deyo Score				< .001
0	13,953 (81)	9096 (82)	2976 (77)	
≥ 1	3306 (19)	1991 (18)	876 (23)	

RT = radiotherapy; IQR = interquartile range; ER = estrogen receptor; PR = progesterone receptor
*Residence setting as defined by the United States Department of Agriculture Economic Research Service (USDA ERS, 2013)[13]

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Table 2 Demographic and Clinicopathologic Details of the Primary Study Population, After PSM.

Demographic Details, n (%)	Overall	RT	NO RT	*P*-value
Age				.965
< 70	663 (21)	332 (21)	331 (21)	
≥ 70	2567 (80)	1283 (79)	1284 (80)	
Sex				.479
Male	8 (0)	3 (0)	5 (0)	
Female	3222 (100)	1612 (100)	1610 (100)	
Race				.913
White	2809 (87)	1405 (87)	1404 (87)	
Black	317 (10)	160 (10)	157 (10)	
Other	104 (3)	50 (3)	54 (3)	
Insurance				.473
Uninsured	23 (1)	12 (1)	11 (1)	
Private	643 (20)	337 (21)	306 (19)	
Medicaid	68 (2)	32 (2)	36 (2)	
Medicare	2444 (76)	1209 (75)	1235 (77)	
Other	24 (1)	15 (1)	9 (1)	
Clinicopathologic Details, n(%)	Overall	RT	NO RT	*P*-value
Laterality				.972
Right	1525 (47)	763 (47)	762 (47)	
Left	1705 (53)	852 (53)	853 (53)	
Tumor size				.817
≤ 2cm	2667 (83)	1331 (82)	1336 (83)	
> 2cm	563 (17)	284 (18)	279 (17)	
ER				.781
ER+	3217 (100)	1608 (100)	1609 (100)	
ER-	13 (0)	7 (0)	6 (0)	
PR				1.000
PR+	3096 (96)	1548 (96)	1548 (96)	
PR-	134 (4)	67 (4)	67 (4)	
HER2				.652
HER2+	45 (1)	24 (2)	21 (1)	
HER2-	3185 (99)	1591 (99)	1594 (99)	
LVI				.750
LVI present	48 (2)	25 (2)	23 (2)	
LVI not present	2749 (98)	1368 (98)	1381 (98)	
Radiotherapy				
Yes	1615 (50)			
No	1615 (50)			
Endocrine Therapy				.822
Yes	2178 (67)	1086 (67)	1092 (68)	
No	1052 (33)	529 (33)	523 (32)	
Chemotherapy				.496
Yes	55 (2)	30 (2)	25 (2)	
No	3175 (98)	1,585 (98)	1590 (99)	
Charlson-Deyo Score				.933
0	2498 (77)	1250 (77)	1248 (77)	
≥ 1	732 (23)	365 (23)	367 (23)	

RT = radiotherapy; IQR = interquartile range; ER = estrogen receptor; PR = progesterone receptor
*Residence setting as defined by the United States Department of Agriculture Economic Research Service (USDA ERS, 2013)[13]

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Table 3 Binary Logistic Regression Analysis for Factors Predicting Adjuvant Radiotherapy.

Variables	OR	95% CI	*P*-value
Age (years)			
0-69	1		
≥ 70	0.170	0.156- 0.185	< .001
Sex			
Male	1		
Female	1.208	0.631- 2.310	.569
Race			
White	1		
Black	1.076	0.953- 1.214	.237
Other	1.355	1.131- 1.623	.001
Insurance			
Uninsured	1		
Private	1.403	0.937- 2.102	.100
Medicaid	1.089	0.693- 1.711	.711
Medicare	0.446	0.299- 0.665	< .001
Other	1.114	0.612- 2.028	.725
Laterality			
Right	1		
Left	0.919	0.854- 0.989	.025
Tumor Size (mm)			
0-20	1		
> 20	1.033	0.930- 1.147	.548
ER			
ER+	0.997	0.682- 1.457	.987
ER-	1		
PR			
PR+	0.942	0.814- 1.090	.424
PR-	1		
HER2			
HER2+	1.851	1.375- 2.493	< .001
HER2-	1		
LVI			
LVI present	1.144	0.827- 1.581	.417
LVI not present	1		
Endocrine Therapy			
Yes	4.023	3.705- 4.368	< .001
No	1		
Chemotherapy			
Yes	3.189	2.582- 3.940	< .001
No	1		
Charlson-Deyo Score			
0	1		
≥1	0.744	0.680- 0.813	< .001

OR = odds ratio; CI = confidence interval; PR = progesterone receptor

(11%) received neither. For patients < 70 years old, 5964 (78%) received both RT and ET, 885 (12%) received only RT, 414 (5%) received only ET, and 392 (5%) received neither. For patients ≥ 70 years old, 3083 (45%) received both RT and ET, 913 (13%) received only RT, 1631 (23%) received only ET, and 1243 (18%) received neither. For patients ≥ 70 years old, radiotherapy use decreased over time ($P < .001$).

Patients who received radiotherapy were younger ($P < .001$), were more likely to be a race other than white or black ($P = .003$), and were more likely to have right-sided disease ($P = .025$). Patients who received radiotherapy had a higher frequency of adjuvant endocrine therapy ($P < .001$) and chemotherapy ($P < .001$), and had a lower number of comorbidities based on the Charlson-Deyo combined comorbidity score [CDCC] ($P < .001$). Most patients who received radiotherapy were privately insured whereas most patients who did not receive radiotherapy were insured by Medicare ($P < .001$) (Table 1). After PSM, treatment cohorts had no difference in demographic or clinicopathologic variables (Table 2).

Patients ≥ 70 years old (OR 0.170; 95% CI 0.156- 0.185), with Medicare (OR 0.446; 95% CI 0.299-0.665), with a left-sided tumor (OR 0.919; 95% CI 0.854- 0.989), and with a CDCC score of 1 or higher (OR 0.744; 95% CI 0.680-0.813) were less likely to have received radiotherapy (Table 3). Patients were more likely to have received radiotherapy if they were of a race other than white or black (OR 1.355; 95% CI 1.131-1.623), had HER2-overexpression (OR 1.851; 95% CI 1.375-2.493), received adjuvant endocrine therapy (OR 4.023; 95% CI 3.705-4.368), or received adjuvant chemotherapy (OR 3.189; 95% CI 2.582-3.940) (Table 3). Gender, tumor size, ER-expression, PR-expression, and lymphovascular invasion (LVI) were not associated with administration of radiotherapy (Table 3).

On UVA following PSM, black race (HR 0.639; 95% CI 0.458-0.893), private insurance (HR 0.242; 95% CI 0.104-0.563), HER2-overexpression (HR 0.390; 95% CI 0.161-0.942), radiotherapy (HR 0.666; 95% CI 0.563-0.788), endocrine therapy (HR 0.814; 95% CI 0.686-0.966), and chemotherapy (HR 0.239; 95% CI 0.077-0.742) were favorable prognostic factors for OS (Table 4). Unfavorable prognostic factors included age ≥ 70 years (HR 3.066; 95% CI 2.245-4.185), tumor size > 20 mm (HR 1.718; 95% CI 1.415-2.087), and CDCC score > 0 (HR 1.706; 95% CI 1.427-2.040). Gender, tumor laterality, ER-expression, PR-expression, and LVI were not prognostic. On MVA following PSM, black race, private insurance, radiotherapy, and endocrine therapy remained favorable prognostic factors for OS while age ≥ 70 years, tumor size > 20 mm, and CDCC score > 0 remained negative prognostic factors. HER2-overexpression and chemotherapy use were no longer prognostic on MVA.

Further subgroup analyses were conducted after stratifying patients by age. On UVA of patients age < 70 years following PSM, private insurance (HR 0.077; 95% CI 0.016-0.364) and radiotherapy (HR 0.395; 95% CI 0.192-0.811) were favorable prognostic factor while age greater than the median of 62 years (HR 3.428; 95% CI 1.599 7.351) and CDCC score > 0 (HR 5.041; 95% CI 2.558-9.937) were unfavorable prognostic factors (Table 5). On MVA, private insurance and radiotherapy remained favorable prognostic factors, Charlson-Deyo comorbidty score > 0 remained an unfavorable prognostic factor, and age was no longer prognostic. On UVA of patients age ≥ 70 years following PSM, black race (HR 0.694; 95% CI 0.482-0.998), private insurance (HR 0.175; 95% CI 0.069-0.443), Medicare (HR 0.274; 95% CI 0.113-0.661), radiotherapy (HR 0.607; 95% CI

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Table 4 Univariate and Multivariate Cox Regression Analyses of OS, after PSM.

	Univariate Analysis			Multivariate Analysis		
Variables	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age (years)						
0-69	1					
≥ 70	3.066	2.245- 4.185	< .001	2.668	1.903- 3.740	< .001
Sex						
Male	1					
Female	1.293	0.322- 5.187	.717			
Race						
White	1					
Black	0.639	0.458- 0.893	.009	0.703	0.498- 0.991	.044
Other	0.829	0.496- 1.386	.474			
Insurance						
Uninsured	1					
Private	0.242	0.104- 0.563	.001	0.184	0.078- 0.432	< .001
Medicaid	0.495	0.180- 1.363	.174			
Medicare	0.605	0.270- 1.354	.221			
Other	0.470	0.118- 1.880	.286			
Laterality						
Right	1					
Left	0.898	0.761- 1.061	.207			
Tumor Size (mm)						
0-20	1					
> 20	1.718	1.415- 2.087	< .001	1.964	1.613- 2.391	< .001
ER						
ER+	4.447	0.625- 31.641	.136			
ER-	1					
PR						
PR+	1.538	0.935- 2.530	.090			
PR-	1					
HER2						
HER2+	0.390	0.161- 0.942	.036	0.505	0.184- 1.389	.186
HER2-	1					
LVI						
LVI present	0.611	0.253- 1.475	.273			
LVI not present	1					
Radiation Therapy						
Yes	0.666	0.563- 0.788	< .001	0.629	0.531- 0.746	< .001
No	1					
Endocrine Therapy						
Yes	0.814	0.686- 0.966	.018	0.676	0.567- 0.805	< .001
No	1					
Chemotherapy						
Yes	0.239	0.077- 0.742	.013	0.553	0.170- 1.797	.325
No	1					
Charlson-Deyo Score						
0	1					
≥ 1	1.706	1.427- 2.040	< .001	1.770	1.474- 2.126	< .001

HR hazard ratio; CI confidence interval; PR progesterone receptor

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Table 5 Univariate and Multivariate Cox Regression Analyses of OS for Age < 70 yrs, after PSM.

	Univariate Analysis			*Multivariate Analysis*		
Variables	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age (years)						
0-62	1					
63-69	3.428	1.599- 7.351	.002	1.844	0.749- 4.543	.183
Race						
White	1					
Black	1.059	0.410- 2.738	.905			
Insurance						
Uninsured	1					
Private	0.077	0.016- 0.364	.001	0.101	0.021- 0.487	.004
Medicaid	0.182	0.030- 1.090	.062			
Medicare	0.406	0.095- 1.736	.224			
Laterality						
Right	1					
Left	1.288	0.645- 2.573	.474			
Tumor Size (mm)						
0-20	1					
> 20	1.140	0.532- 2.443	.737			
ER						
ER+	0.853	0.116- 6.268	.876			
ER-	1					
PR						
PR+	1.953	0.596- 6.398	.269			
PR-	1					
HER2						
HER2+	0.041	0.000- 4.136	.175			
HER2-	1					
Radiation Therapy						
Yes	0.395	0.192- 0.811	.011	0.447	0.214- 0.930	.031
No	1					
Endocrine Therapy						
Yes	1.105	0.558- 2.189	.774			
No	1					
Chemotherapy						
Yes	0.863	0.334- 2.234	.762			
No	1					
Charlson-Deyo Score						
0	1					
≥1	5.041	2.558- 9.937	< .001	3.858	1.919- 7.757	< .001

HR = hazard ratio; CI = confidence interval; PR = progesterone receptor

0.510-0.724), and endocrine therapy (HR 0.658; 95% CI 0.551-0.786) were favorable prognostic factors while age greater than the median of 77 years (HR 2.147; 95% CI 1.794-2.569), tumor size > 20 mm (HR 1.856; 95% CI 1.518-2.269), and CDCC score > 0 (HR 1.591; 95% CI 1.319-1.920) were unfavorable prognostic factors (Table 6). These factors also remained prognostic on MVA.

After PSM, 5 year OS for the primary study population was 86% for those who received RT and 81% for those who did not (P < .001) (Figure 2). Patients < 70 years old who received radiotherapy were observed to have a 5 year OS advantage (97% vs. 92%, P = .009) compared to those who did not. Patients ≥70 years old who received radiotherapy were also observed to have a 5-year OS advantage (85% vs. 78%, P < 0.001) compared to those who did not.

To account for the potential confounding effects of comorbidities on OS, patients from the primary study population were stratified by CDCC score of 0 versus ≥ 1. Kaplan-Meier analysis showed that a 5 year OS advantage with radiotherapy existed for patients with a CDCC score of 0 (5 year OS 88% with radiotherapy vs. 84%

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Table 6 Univariate and Multivariate Cox Regression Analyses of OS for Age ≥ 70 yrs, after PSM.

	Univariate Analysis			*Multivariate Analysis*		
Variables	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age (years)						
70-77	1					
≥78	2.147	1.794- 2.569	< .001	1.807	1.497- 2.180	< .001
Race						
White	1					
Black	0.694	0.482- 0.998	.049	0.675	0.465- 0.979	.038
Insurance						
Uninsured	1					
Private	0.175	0.069- 0.443	< .001	0.188	0.073- 0.484	.001
Medicaid	0.323	0.098- 1.059	.062			
Medicare	0.274	0.113- 0.661	.004	0.275	0.112- 0.676	.005
Laterality						
Right	1					
Left	0.887	0.745- 1.055	.174			
Tumor Size (mm)						
0-20	1					
>20	1.856	1.518- 2.269	< .001	1.907	1.552- 2.343	< .001
ER						
ER+	1.301	0.183- 9.259	.792			
ER-	1					
PR						
PR+	1.141	0.683- 1.908	.615			
PR-	1					
HER2						
HER2+	0.829	0.343- 2.004	.677			
HER2-	1					
Radiation Therapy						
Yes	0.607	0.510- 0.724	< .001	0.669	0.558- 0.802	< .001
No	1					
Endocrine Therapy						
Yes	0.658	0.551- 0.786	< .001	0.651	0.542- 0.781	< .001
No	1					
Chemotherapy						
Yes	0.703	0.175- 2.820	.619			
No	1					
Charlson-Deyo Score						
0	1					
≥ 1	1.591	1.319- 1.920	< .001	1.815	1.499- 2.198	< .001

HR = hazard ratio; CI = confidence interval; PR = progesterone receptor

without, $P < 0.001$), as well as those with a score ≥ 1 (82% with radiotherapy vs. 73% without, $P < 0.001$).

Discussion

This is the largest study to date investigating the impact of postoperative radiation following BCS in patients with PMBC. The present results indicate that there is an OS benefit associated with postoperative radiation, suggesting that radiotherapy should remain the standard of care for these patients. After multiple stratifications, the benefit in OS remained for all patients including those ≥ 70 years old.

Recent genetic and immune profiling studies have delineated differences between PMBC and the more common ER positive HER2 negative invasive ductal carcinoma (IDC) of the breast.[15] These studies have shown that PMBC has lower genomic instability, decreased rates of PIK3CA and TP53 mutations, lower tumor infiltrating lymphocyte levels (TIL), and increased expression of MUC2 and MUC4 than IDC.[15-16] PMBC have aberrant DNA methylation of MUC2 which may be the driver for production of extracel-

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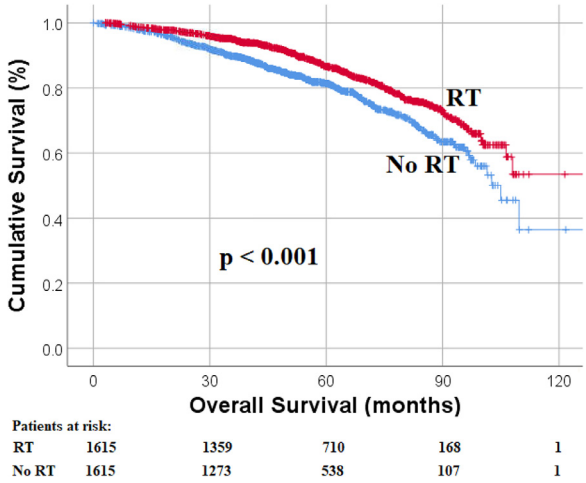
Figure 2 Kaplan-Meier curves for OS, after PSM. Censored patients are represented on the curves by vertical tick marks.



lular mucin in PMBC.[15-16] Higher MUC2 levels have been shown to increase resistance to chemotherapy and furthermore it has been suggested that the extracellular mucin acts as a barrier to immune recognition and may therefore be responsible for the low TILs in PMBC.[17-18] Since mucin appears to protect PMBC against systemic therapy and the immune system, radiotherapy would be a method to circumvent this barrier.

This study is among the first to indicate an OS advantage with the use of postoperative radiotherapy for patients with PMBC receiving BCS. Notably, the findings of our study are supported by a Surveillance, Epidemiology and End Results (SEER) database study of 3416 patients ≥ 65 years old with mucinous carcinoma which found that postoperative radiotherapy following BCS significantly improved breast cancer-specific survival (Table 7).[9] Furthermore, a prospective single-arm trial included patients with mucinous and tubular breast cancer with favorable characteristics and found that BCS without adjuvant radiotherapy resulted in a 23% local recurrence rate at a median follow-up of 7 years.[19] These 2 studies in conjunction with our study suggest that omission of radiotherapy following BCS in patients with mucinous carcinoma may lead to worse clinical outcomes.

In the modern era, there has been an effort to identify patients for whom it is safe to omit radiotherapy following breast conserving surgery. CALGB 9343 was a randomized controlled trial which showed that for patients ≥ 70 years old with cT1N0M0, ER-positive breast cancer of any histology, there was no improvement in OS with radiation following BCS.[20] Although these findings appear to dispute the findings of our study regarding patients ≥ 70 years old, this trial involved only patients with tumors < 2 cm and required administration of endocrine therapy for at least 5 years while our study included tumors of any size, did not exclude patients who did not receive endocrine therapy, and could not evaluate adherence to endocrine therapy. Two major critiques of CALGB 9343 include the criticality of endocrine therapy adherence and the failure to compare endocrine therapy without radiation therapy to radiation therapy without endocrine therapy. The former critique was recently highlighted by Showalter et al. who used the SEER database to show that in the cohort of patients who omit radiotherapy, those adherent to endocrine therapy had lower recurrence than those nonadherent to endocrine therapy.[21] The latter critique was recently highlighted by Buszek et al. who used the NCDB database to show that omission of radiation therapy with administration of endocrine therapy results in equivalent survival to omission of endocrine therapy with administration of radiation therapy.[22] Compliance with 5 years of endocrine therapy is often poor due to side effects and patients not wanting to take medication, so radiation may be easier to tolerate and of shorter duration. The implications of our study support radiotherapy after BCS for PMBC and patients ≥ 70 years old should also be offered radiation.[23-24]

In the present study, 42% of patients ≥ 70 years old did not receive RT. This rate is much higher than prior NCDB.[22] We suspect the reason for this is PMBC has been historically considered more favorable so these patients may be less likely to be dispositioned to RT.

Notably, although endocrine therapy was a favorable prognostic factor in the present study on both UVA and MVA in the overall population, after stratifying the population by age these results only remained for patients ≥ 70 years old. The reason for this is less clear and could be due to the differences in adjuvant endocrine therapy guidelines for premenopausal woman and postmenopausal woman, since the younger cohort certainly contains both groups of women. It could also be due to a selection bias in which older women only received endocrine therapy if they had a better performance status and less medical comorbidities. Given that the median tumor size in this study cohort was 13 mm with 94.6% of tumors measuring < 3 cm, in addition to the fact that this cohort was entirely node negative, a majority of these patients would not have explicitly required endocrine therapy per current NCCN treatment guidelines.[8] Yet endocrine therapy was a favorable prognostic factor in

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Table 7 Clinicopathologic Details and Survival Outcomes of Mucinous Carcinoma Patients in This Study Versus Prior Studies.

Study Details						
Authors	*Current Study*			*Wu SG, et al.*		
Reference #	-			9		
Year of Publication	-			2019		
Study Type	NCDB Database			SEER Database		
Number of PMBC Patients	17,259			3,416		
Age (years)						
Median	69			75		
Range	22-90			65-99		
CLINICOPATHOLOGIC DETAILS, n (%)	OVERALL	RT	NO RT	OVERALL	RT	NO RT
ER						
ER+	16,838 (99)	10,877 (99)	3706 (99)	3416 (100)	2191 (64)	1225 (36)
ER-	162 (1)	106 (1)	36 (1)	0 (0)	0 (0)	0 (0)
PR						
PR+	15,725 (93)	10,148 (93)	3477 (93)	3416 (100)	2191 (64)	1225 (36)
PR-	1,218 (7)	793 (7)	256 (7)	0 (0)	0 (0)	0 (0)
HER2						
HER2+	390 (3)	271 (4)	53 (2)	-	-	-
HER2-	11,752 (97)	7462 (97)	2702 (98)	-	-	-
Radiotherapy						
Yes	11,087 (74)	11,087 (74)	0 (0)	2,191 (64)	2,191 (64)	-
No	3852 (26)	0 (0)	3852 (26)	1225 (36)	-	1225 (36)
Endocrine Therapy						
Yes	12,774 (77)	9,047 (83)	2,045 (56)	-	-	-
No	3923 (24)	1798 (17)	1635 (44)	-	-	-
Chemotherapy						
Yes	1124 (7)	872 (8)	99 (3)	73 (2)	61 (3)	12 (1)
No	15,770 (94)	10,047 (92)	3638 (97)	3343 (98)	2130 (97)	1213 (99)
Median Follow-up (months)	64			95		
SURVIVAL OUTCOMES	OVERALL	RT	NO RT	OVERALL	RT	NO RT
Overall Survival (%)						
5-year	-	86	81	-	-	-
10-year	-	-	-	-		
Cancer Specific Survival (%)						
5-year	-	-	-	-	-	-
10-year	-	-	-	-	98	95

the overall study population, suggesting that further study regarding the prognostic implications of endocrine therapy in patients with mucinous carcinoma is indicated.

As expected, older age, larger tumor size, and higher comorbidity score were all negative prognostic factors for OS in this study. It is unclear why black race was a positive prognostic factor in the overall cohort and the elderly cohort. In the overall breast cancer population irrespective of histology, black race is a known negative prognostic factor.[25] Because PMBC is a distinct entity from other breast carcinomas, we speculate that the disease process in patients of black race may be different from other races and we acknowledge that further studies on this topic are necessary. Lastly, the patients with private insurance in all cohorts and the patients with Medicare in the elderly cohort both had an improved OS compared to the uninsured, which may be due to better access to health care.

This study has some limitations that inherently accompany database studies such as inconsistent reporting, missing data, and lack of detailed comorbidity data. Because there was no central review of pathology, this study assumes all involved pathologists utilized a uniform definition of PMBC. Furthermore, assessment that an invasive carcinoma has greater than 90% mucinous component is subjective. The NCDB neither specifies cancer-specific death versus death from other causes, nor does it include data on local tumor recurrence. Data regarding the type of chemotherapy and endocrine therapy and the length of its use are not available. The Charlson-Deyo comorbidity score is a summative measure of a patient's comorbidities, accounting for a majority of the most serious comorbidities including myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, diabetes mellitus, renal disease, and liver disease. However, it does not allow for the analysis of specific individual comorbidities, and

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it is possible that comorbid conditions could have been underreported. Patients with certain comorbidities may not have received radiotherapy at all or as frequently, which could confound the findings of this study. This was addressed by stratifying the patient population based on Charlson-Deyo score of 0 versus ≥ 1 and still demonstrating a consistent 5-year OS advantage with radiotherapy.

Ultimately, the findings of this study suggest that postoperative radiotherapy is associated with a survival advantage in patients with pN0 cM0 mucinous carcinoma who received BCS, including patients who are ≥ 70 years old. These findings suggest that omission of radiotherapy from locoregional treatment of patients with PMBC is not warranted. Future studies on mucinous carcinoma that include local recurrence data, disease specific survival data, and more specific comorbidity data would be helpful to confirm the results of the present study.

Clinical Practice Points

- Pure mucinous breast carcinoma is a low-grade histology with favorable prognosis.
- Post-lumpectomy radiotherapy is associated with overall survival benefit for pure mucinous breast carcinoma.
- Adjuvant radiotherapy should remain standard of care for pure mucinous breast carcinoma.

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Disclosure

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

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