Outcomes in Nonmetastatic Hormone Receptor–Positive HER2-Negative Pure Mucinous Breast Cancer: A Multicenter Cohort Study

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Abstract

Background: Although considered a favorable subtype, pure mucinous breast cancer (PMBC) can recur, and evidence for adjuvant therapy is limited. We aimed to compare outcomes of nonmetastatic PMBC with invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) to address these uncertainties. **Methods:** Individual patient-level data from 6 centers on stage I–III hormone receptor–positive and HER2-negative PMBC, IDC, and ILC were used to analyze recurrence-free interval (RFI), recurrence-free survival (RFS), and overall survival (OS), and to identify prognostic factors for PMBC. **Results:** Data from 20,684 IDC cases, 1,475 ILC cases, and 943 PMBC cases were used. Median follow-up was 6.6 years. Five-year RFI, RFS, and OS for PMBC were 96.1%, 94.9%, and 98.1%, respectively. On multivariable Cox regression, PMBC demonstrated superior RFI (hazard ratio [HR], 0.59; 95% CI, 0.43–0.80), RFS (HR, 0.70; 95% CI, 0.56–0.89), and OS (HR, 0.71; 95% CI, 0.53–0.96) compared with IDC. ILC showed comparable outcomes to IDC. Fewer than half (48.7%) of recurrences in PMBC were distant, which was a lower rate than for IDC (67.3%) and ILC (80.6%). In contrast to RFI, RFS events were driven more by non–breast cancer deaths in older patients. Significant prognostic factors for RFI among PMBC included positive lymph node(s) (HR, 2.42; 95% CI, 1.08–5.40), radiotherapy (HR, 0.44; 95% CI, 0.23–0.85), and endocrine therapy (HR, 0.25; 95% CI, 0.09–0.70). No differential chemotherapy associations with outcomes were detected across PMBC subgroups by nodal stage, tumor size, and age. A separate SEER database analysis also did not find any association of improved survival with adjuvant chemotherapy in these subgroups. **Conclusions:** Compared with IDC, PMBC demonstrated superior RFI, RFS, and OS. Lymph node negativity, adjuvant radiotherapy, and endocrine therapy were associated with superior RFI. Adjuvant chemotherapy was not associated with better outcomes.

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Background

Mucinous breast carcinoma (MuBC) is the third most common histologic subtype of breast cancer (BC) (~3% of invasive BCs), after invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). MuBC has a better prognosis in studies from both the West and Asia, where its incidence is more common than ILC in women aged <40 years.[1–4] The 2019 WHO classification of tumors of the breast characterizes MuBC primarily by the production and extracellular presence of mucin.[5] MuBC can be classified into pure MuBC (PMBC) and mixed MuBC.[6] PMBC is more frequently encountered and is pathologically defined as tumor cells suspended in extracellular mucin in >90% of the tumor.[7]

Although PMBC is considered a favorable subtype, recurrence can occur. In a study of 7,372 patients diagnosed with immunohistochemically defined luminal invasive BC, disease-free survival of 143 patients with mucinous tumors was reported to be similar to that of 5,707 with IDC (5-year disease-free survival, 93% vs 87.4%; hazard ratio [HR], 1.03; $P = .91$). Overall survival (OS) was significantly worse than IDC in the subgroup of patients with luminal A carcinomas (HR, 2.96; 95% CI, 1.26–6.95; $P = .01$).[8]

Current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer recommend consideration of adjuvant chemotherapy only for node-positive

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tumors, whereas adjuvant endocrine therapy (ET) is recommended for estrogen receptor (ER)–positive and/or progesterone receptor (PR)–positive node-positive tumors or tumors ≥3 cm, and may be considered for ER-positive and/or PR-positive tumors measuring 1.0 to 2.9 cm.[9] However, there is no level 1 evidence from randomized clinical trials on PMBC for these recommendations. A prior Korean BC Registry study by Kim et al[10] of 3,076 patients with early-stage MuBC reported no BC-specific survival (BCSS) or OS association with adjuvant chemotherapy. In contrast, a SEER database propensity score matching analysis by Gao et al[11] of 805 pairs of patients with MuBC who did or did not receive adjuvant chemotherapy found an improved OS but not BCSS for adjuvant chemotherapy in patients with positive lymph node(s) (LN[s]) or tumors >3 cm. As prior studies did not always have details on HER2 status, ET, and relapse events, further contemporary studies with such data would be helpful to address this uncertainty.

Our study aims were to compare the recurrence and survival outcomes of PMBC against IDC and ILC, identify the clinicopathologic prognostic factors of PMBC, and explore the association of adjuvant systemic therapy with outcomes across subgroups of PMBC defined by nodal status, tumor size, and age in an international multicenter cohort study as well as the SEER database.

Methods

Study Participants and Design

Female patients diagnosed in January 2000 through December 2015 with hormone receptor (HR)–positive HER2-negative stage I–III PMBC, IDC, and ILC who underwent primary breast surgery at 6 academic institutions in Singapore, Taiwan, Korea, and Japan were evaluated. The details of data from each study center, including the years covered by each registry, are summarized in Table S1 in the supplementary materials (available online with this article). The study was approved by the respective ethics committees of participating institutions.

The SEER study cohort was extracted through SEERStat from SEER Research Data 17 Registries Nov 2022 Sub (2000–2020). Female patients diagnosed in January 2000 through December 2015 with HR-positive HER2-negative stage I–III PMBC who underwent breast surgery were included. The data cutoff for this cohort was December 31, 2020.

Variables and Outcome Measures

Extracted information included patient demographics, tumor characteristics (including ER, PR, HER2 immunohistochemistry, and HER2 in situ hybridization status based on the prevailing ASCO/College of American Pathologists [CAP] recommendations),[12–15] and treatment administered.[16] All BCs were staged pathologically according to the 5th, 6th, or 7th edition of the AJCC TNM classifications, which were generally adopted within 3 months after their publication.[17–19] Clinical staging was used for patients who received neoadjuvant therapy. Outcome measures were recurrence-free interval (RFI), recurrence-free survival (RFS), and OS, each defined according to Standardized Definitions for Efficacy End Points version 2.[20] We chose to include RFI to focus on BC-related events, because RFS also includes non-BC deaths. For the SEER cohort, information on ET was not available, and patients who did not have chemotherapy or with unknown chemotherapy status were grouped together. RFI and RFS were also not available; thus, OS and BCSS were used as outcome measures for the SEER cohort.

Statistical Analyses

Categorical and continuous characteristics between histology subtype groups were compared using Fisher exact test and the Kruskal-Wallis test, respectively. Follow-up duration was estimated using the reverse Kaplan-Meier method. RFI, RFS, and OS were estimated using the Kaplan-Meier method. The association of each survival outcome with each characteristic was assessed via the Cox proportional hazard model and tested using Wald's test. Proportional hazard assumption was verified based on Schoenfeld residuals. Characteristics with univariable $P<.10$ were selected for fitting of multivariable models. Each fitted multivariable Cox model was not adjusted by study center given that there was no evidence of high heterogeneity in all survival outcomes across study centers. Heterogeneity in survival outcomes was assessed using the index of heterogeneity (I^2), which was generated by pooling the univariable HR estimate from each study center with a random effect–restricted maximum likelihood estimation model. Exploratory subgroup analyses were further conducted to assess the heterogeneity of chemotherapy/ET associations by age group (<50 vs ≥50 years) and NCCN Guideline categories defined based on nodal status and tumor size; these analyses were performed by including an interaction term between receipt of chemotherapy/ET and each subgroup variable in the Cox model. Subgroup analyses by NCCN Guideline categories based on the multicenter cohort were age-adjusted, and corresponding analyses of the SEER cohort were further adjusted for additional covariates as specified in the result tables.

No imputation for missing values was performed. There was a high extent of missing values (>10%) for tumor grade among the PMBC in the multicenter cohort; their impact on identified prognostic factors of PMBC was evaluated via sensitivity analyses in which the final multivariable model for each survival outcome was refitted excluding tumor grade. Analyses were performed using SAS 9.4 (SAS Institute Inc) and Stata, version 16.0 (StataCorp LLC). All statistical tests were 2-sided with a 5% significance level.

Results

Clinical and Treatment Characteristics

A total of 23,102 women in the multicenter cohort were identified for analysis (Supplementary Figure S1), of which 20,684 (89.5%) had IDC, 1,475 (6.4%) had ILC, and 943 (4.1%) had PMBC. Clinicopathologic and treatment characteristics by histologic subtype are shown in Table 1. More prominent differences between PMBC versus IDC and ILC included its higher percentage of patients aged <40 years (20.7% vs 12.5% vs 5.3%, respectively; $P<.001$) and with LN-negative tumors (87.9% vs 62.7% vs 60.1%, respectively; $P<.001$). Among patients with PMBC, 24.9% received chemotherapy, which was less than half that in patients with IDC (55.1%) and ILC (56.6%).

Recurrence and Survival Outcomes

Median follow-up was 6.6 years (IQR, 5.0–9.0 years). The 5-year RFI, RFS, and OS for PMBC were 96.1% (95% CI, 94.6%–97.2%), 94.9% (95% CI, 93.1%–96.1%), and 98.1% (95% CI, 97.0%–98.9%), respectively (Figure 1). There was no evidence of high heterogeneity

Table 1. Clinicopathologic and Treatment Characteristics by Histologic Subtype

	Total n (%)	IDC n (%)	ILC n (%)	PMBC n (%)	*P* Value[a]
Total	23,102 (100.0)	20,684 (100.0)	1,475 (100.0)	943 (100.0)	
Age at diagnosis					<.001
<40 y	2,897 (12.5)	2,624 (12.7)	78 (5.3)	195 (20.7)	
40–49 y	9,269 (40.1)	8,310 (40.2)	586 (39.7)	373 (39.6)	
50–59 y	5,923 (25.6)	5,303 (25.6)	463 (31.4)	157 (16.6)	
60–69 y	3,407 (14.7)	3,068 (14.8)	241 (16.3)	98 (10.4)	
≥70 y	1,606 (7.0)	1,379 (6.7)	107 (7.3)	120 (12.7)	
Median (IQR), y	49 (43–58)	49 (43–58)	50 (46–59)	47 (41–58)	<.001
Ethnicity					<.001
Chinese	8,287 (35.9)	7,288 (35.2)	595 (40.3)	404 (42.8)	
Korean	9,872 (42.7)	8,907 (43.1)	632 (42.8)	333 (35.3)	
Japanese	3,990 (17.3)	3,665 (17.7)	156 (10.6)	169 (17.9)	
Malay/Indian/Others[b]	953 (4.1)	824 (4.0)	92 (6.2)	37 (3.9)	
Year of diagnosis					<.001
2000–2005	2,351 (10.2)	2,143 (10.4)	110 (7.5)	98 (10.4)	
2006–2010	8,241 (35.7)	7,439 (36.0)	465 (31.5)	337 (35.7)	
2011–2015	12,510 (54.2)	11,102 (53.7)	900 (61.0)	508 (53.9)	
T stage					<.001
T1	13,291(57.5)	12,198 (59.0)	603 (40.9)	490 (52.0)	
T2	8,345 (36.1)	7,337 (35.5)	631 (42.8)	377 (40.0)	
T3	977 (4.2)	700 (3.4)	215 (14.6)	62 (6.6)	
T4	337 (1.5)	305 (1.5)	20 (1.4)	12 (1.3)	
Others (TX, T0)	76 (0.3)	73 (0.4)	3 (0.2)	—	
Missing	76 (0.3)	71 (0.3)	3 (0.2)	2 (0.2)	
N stage					<.001
N0	14,676 (63.5)	12,960 (62.7)	887 (60.1)	829 (87.9)	
N1	5,797 (25.1)	5,353 (25.9)	348 (23.6)	96 (10.2)	
N2	1,675 (7.3)	1,544 (7.5)	119 (8.1)	12 (1.3)	
N3	928 (4.0)	803 (3.9)	120 (8.1)	5 (0.5)	
NX	26 (0.1)	24 (0.1)	1 (0.1)	1 (0.1)	
Overall cancer stage					<.001
I	10,241 (44.3)	9,276 (44.8)	495 (33.6)	470 (49.8)	
II	9,547 (41.3)	8,452 (40.9)	667 (45.2)	428 (45.4)	
III	3,314 (14.3)	2,956 (14.3)	313 (21.2)	45 (4.8)	
ER status					<.001
Positive	22,537 (97.6)	20,136 (97.4)	1,465 (99.3)	936 (99.3)	
Negative	559 (2.4)	543 (2.6)	9 (0.6)	7 (0.7)	
Missing	6 (0.0)	5 (0.0)	1 (0.1)	—	
PR status					<.001
Positive	19,792 (85.7)	17,716 (85.7)	1,222 (82.8)	854 (90.6)	
Negative	3,287 (14.2)	2,948 (14.3)	250 (16.9)	89 (9.4)	
Missing	23 (0.1)	20 (0.1)	3 (0.2)	—	
Tumor grade					<.001
Grade 1 (well differentiated)	5,937 (25.7)	5,179 (25.0)	320 (21.7)	438 (46.4)	
Grade 2 (moderately differentiated)	11,071 (47.9)	10,132 (49.0)	697 (47.3)	242 (25.7)	
Grade 3 (poorly differentiated)	4,765 (20.6)	4,662 (22.5)	87 (5.9)	16 (1.7)	
Missing	1,329 (5.8)	711 (3.4)	371 (25.2)	247 (26.2)	
Received radiotherapy					.002
No	7,355 (31.8)	6,543 (31.6)	464 (31.5)	348 (36.9)	
Yes	14,056 (60.8)	12,649 (61.2)	889 (60.3)	518 (54.9)	
Missing	1,691 (7.3)	1,492 (7.2)	122 (8.3)	77 (8.2)	
Received endocrine therapy					.001
No	1,187 (5.1)	1,100 (5.3)	49 (3.3)	38 (4.0)	
Yes	20,971 (90.8)	18,725 (90.5)	1,368 (92.7)	878 (93.1)	
Missing	944 (4.1)	859 (4.2)	58 (3.9)	27 (2.9)	
Received chemotherapy					<.001
No	10,162 (44.0)	8,891 (43.0)	598 (40.5)	673 (71.4)	
Yes	12,470 (54.0)	11,400 (55.1)	835 (56.6)	235 (24.9)	
Missing	470 (2.0)	393 (1.9)	42 (2.8)	35 (3.7)	

Abbreviations: ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PMBC, pure mucinous breast cancer; PR, progesterone receptor.
[a]Based on Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.
[b]Malay ethnicity: n=477; Indian ethnicity: n=320; other minority ethnicities: n=156.

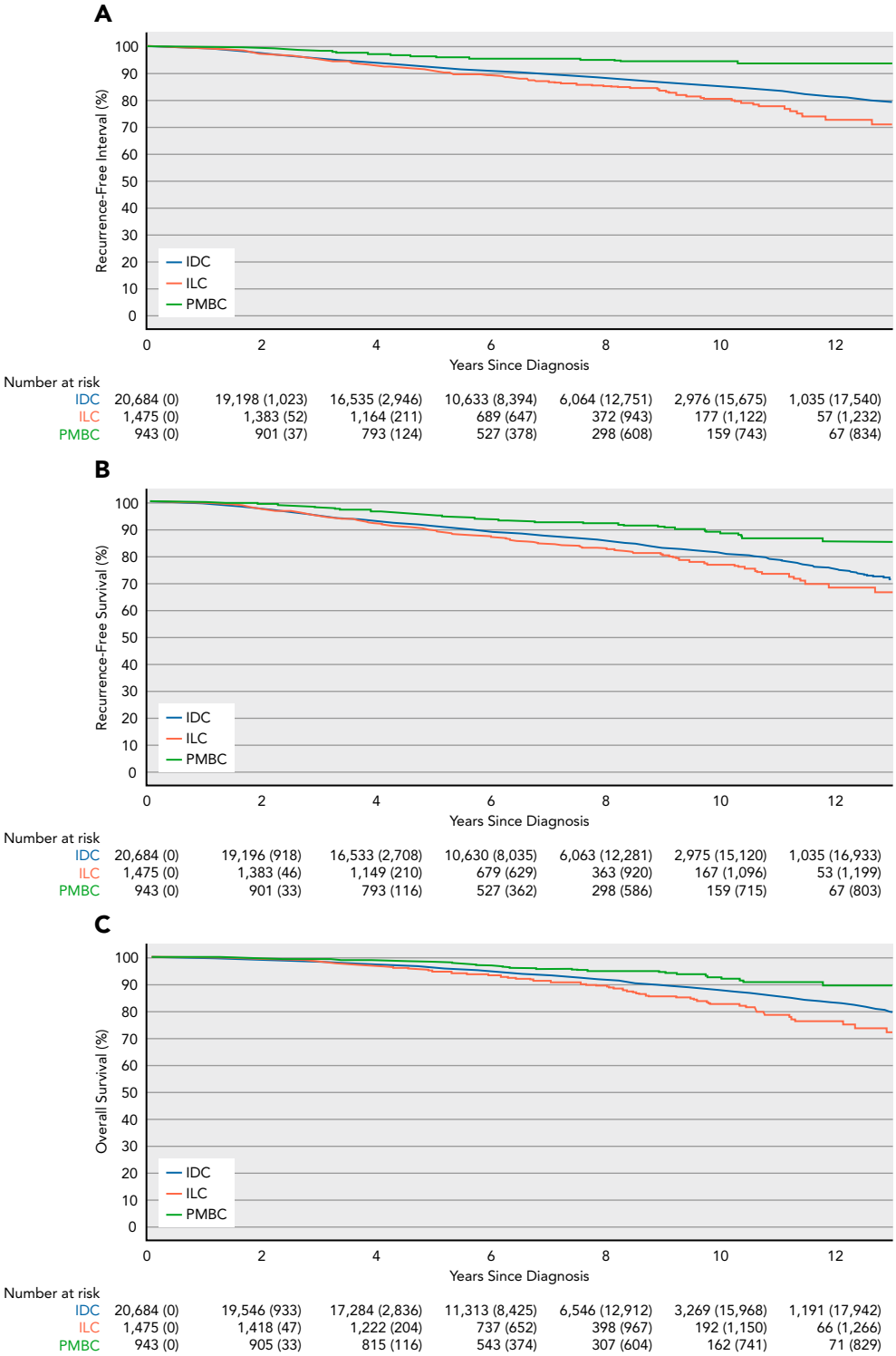

Figure 1. Kaplan-Meier curves of **(A)** recurrence-free interval, **(B)** recurrence-free survival, and **(C)** overall survival by histology subtype.
Abbreviations: HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PMBC, pure mucinous breast cancer.

in all survival outcomes across study centers (RFI I^2, 0%–35%; RFS I^2, 0%; OS I^2, 0%–24.4%). On multivariable Cox regression analyses, PMBC demonstrated superior RFI (HR, 0.59; 95% CI, 0.43–0.80), RFS (HR, 0.70; 95% CI, 0.56–0.89), and OS (HR, 0.71; 95% CI, 0.53–0.96) compared with IDC. ILC had comparable survival outcomes to IDC (Table 2). A total of 2,196 (9.5%) patients had relapsed at the time of analysis. Approximately half of recurrences in PMBC were distant (48.7%), and this was lower than corresponding percentages for IDC (67.3%) and ILC (80.6%) ($P<.001$).

Table 2. Multivariable Cox Regression of RFI, RFS, and OS by Histologic Subtype

	RFI			RFS			OS			Recurrence			
	Events/ Patients	aHR[a] (95% CI)	*P* Value[b]	Events/ Patients	aHR[a] (95% CI)	*P* Value[b]	Events/ Patients	aHR[a] (95% CI)	*P* Value[b]	Total (%)	Local/ Regional (%)	Distant (%)	Missing (%)
IDC	2,158/ 20,268	Ref		2,828/ 20,684	Ref		1,655/ 20,684	Ref		2,002 (100.0)	635 (31.7)	1,347 (67.3)	20 (1.0)
ILC	190/ 1,475	1.10 (0.93–1.29)	.267	227/ 1,475	1.00 (0.87–1.16)	.993	151/ 1,475	1.04 (0.87–1.25)	.654	155 (100.0)	29 (18.7)	125 (80.6)	1 (0.6)
PMBC	44/ 943	0.59 (0.43–0.80)	.001	80/943	0.70 (0.56–0.89)	.003	49/943	0.71 (0.53–0.96)	.024	39 (100.0)	19 (48.7)	19 (48.7)	1 (2.6)

Abbreviations: aHR, adjusted hazard ratio; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; OS, overall survival; PR, progesterone receptor; PMBC, pure mucinous breast cancer; RFI, recurrence-free interval; RFS, recurrence-free survival.
[a]Adjusted for age at diagnosis, ethnicity, year of diagnosis, T stage, N stage, ER status, PR status, tumor grade, and receipt of radiotherapy, endocrine therapy, and chemotherapy.
[b]Based on Wald's test.

Prognostic Factors of PMBC

When restricted to only PMBC, statistically significant independent prognostic factors for RFI included positive LN(s) (HR, 2.42; 95% CI, 1.08–5.40), radiotherapy (HR, 0.44; 95% CI, 0.23–0.85), and ET (HR, 0.25; 95% CI, 0.09–0.70) (Figure 2A, Supplementary Table S2). Similar independent prognostic factors were identified for RFS but also included older age (≥70 vs <50 years: HR, 2.98; 95% CI, 1.75–5.10), ethnicity (others [non-Chinese/Japanese/Korean, mainly Malay and Indian] vs Chinese: HR, 2.52; 95% CI, 1.17–5.43), and tumor size (T3–4 vs T1–2: HR, 2.14; 95% CI, 1.17–3.91) (Figure 2B, Supplementary Table S3). In comparison, significant independent prognostic factors for OS only included older age (≥70 vs <50 years: HR, 7.21; 95% CI, 3.32–15.7), ethnicity (others vs Chinese: HR, 2.99; 95% CI, 1.25–7.20), and tumor size (T3–4 vs T1–2: HR, 2.89; 95% CI, 1.40–5.98) (Figure 2C, Supplementary Table S4). It is worth noting that non-BC deaths comprised 60.7% of all RFS events among patients aged ≥70 years compared with 30.8% in patients aged <70 years. All of these results remained broadly similar in the sensitivity analysis where tumor grade was excluded in fitting of multivariable models for the identification of prognostic factors (results not shown).

Exploratory Subgroup Analyses of Chemotherapy Associations With Outcomes in PMBC

Use of chemotherapy was not identified as an independent prognostic factor for all survival outcomes among PMBC overall (Figure 2). No differential chemotherapy associations were detected in various patient subgroups defined by the NCCN Guidelines at the time of this study (Version 4.2023) on systemic adjuvant treatment of favorable histologies (LN-positive, axillary LN metastases <2 mm or LN-negative, and stratified by tumor size: <1.0, 1.0–2.9, and ≥3.0 cm) as well as age group (Table 3).

Exploratory Subgroup Analysis of Chemotherapy Associations With Outcomes in the SEER PMBC Cohort

A total of 5,414 women were identified for analysis by clinicopathologic and treatment characteristics (Supplementary Tables S5 and S6). Median follow-up was 7.6 years (IQR, 6.1–9.3 years). There was no significant association for OS with chemotherapy in patient subgroups defined by the NCCN Guidelines (Version 4.2023) for systemic adjuvant treatment of favorable histologies (Table 4). A significant association for superior OS, but not BCSS, was observed with chemotherapy in patients aged >50 years. A significant association for inferior BCSS with chemotherapy was seen in the subgroup with tumors ≥3.0 cm (HR, 4.94; 95% CI, 2.30–10.57).

Exploratory Subgroup Analyses of ET Associations With Outcomes in PMBC

In our multicenter cohort, use of ET appeared to be associated with superior outcomes for tumors that were LN-positive or ≥1 cm but N0/N1mic (Supplementary Table S7).

Discussion

This international multicenter cohort study on PMBC evaluated one of the largest contemporary real-world datasets for clinical prognostic factors, which also includes valuable data on relapse events, associations of adjuvant systemic therapy, and a comparison with the SEER database. In our cohort, as anticipated, PMBC showed superior RFI, RFS, and OS compared with IDC and ILC, which both had comparatively similar survival outcomes.

Although prognosis is generally favorable for PMBC, the risk of relapse persists for a small percentage of patients. We found that just under half of recurrences in PMBC were distant (48.7%), which was lower than for IDC or ILC (67.3% and 80.6%, respectively) (Table 2). Recent molecular studies have identified a genomic landscape distinct from IDCs, with PMBC having less genomic instability and decreased prevalence of *PIK3CA* and *TP53* mutations as well as fewer concurrent 1q gains and 16q losses.[21,22] More recently, another study reported that *HYDIN* (axonemal central pair apparatus protein) is the most frequently mutated gene (88%) from the whole-exome sequencing of 8 PMBCs.[23] These findings may partly explain its distinct biology with relative chemoresistance. Predictive biomarkers and specific therapeutics are still needed for this understudied subtype, underscored by the finding that 14 (35.9%) of the patients with relapsed PMBC had received prior chemotherapy.[21,22,24]

LN positivity, adjuvant radiotherapy, and ET were the only significant independent prognostic factors for RFI of PMBCs on multivariable analyses. These same factors were also associated with superior RFS but not superior OS (Figure 2). It is worth noting that in our study, the inferior RFS and OS in older patients were driven largely by non-BC deaths rather than

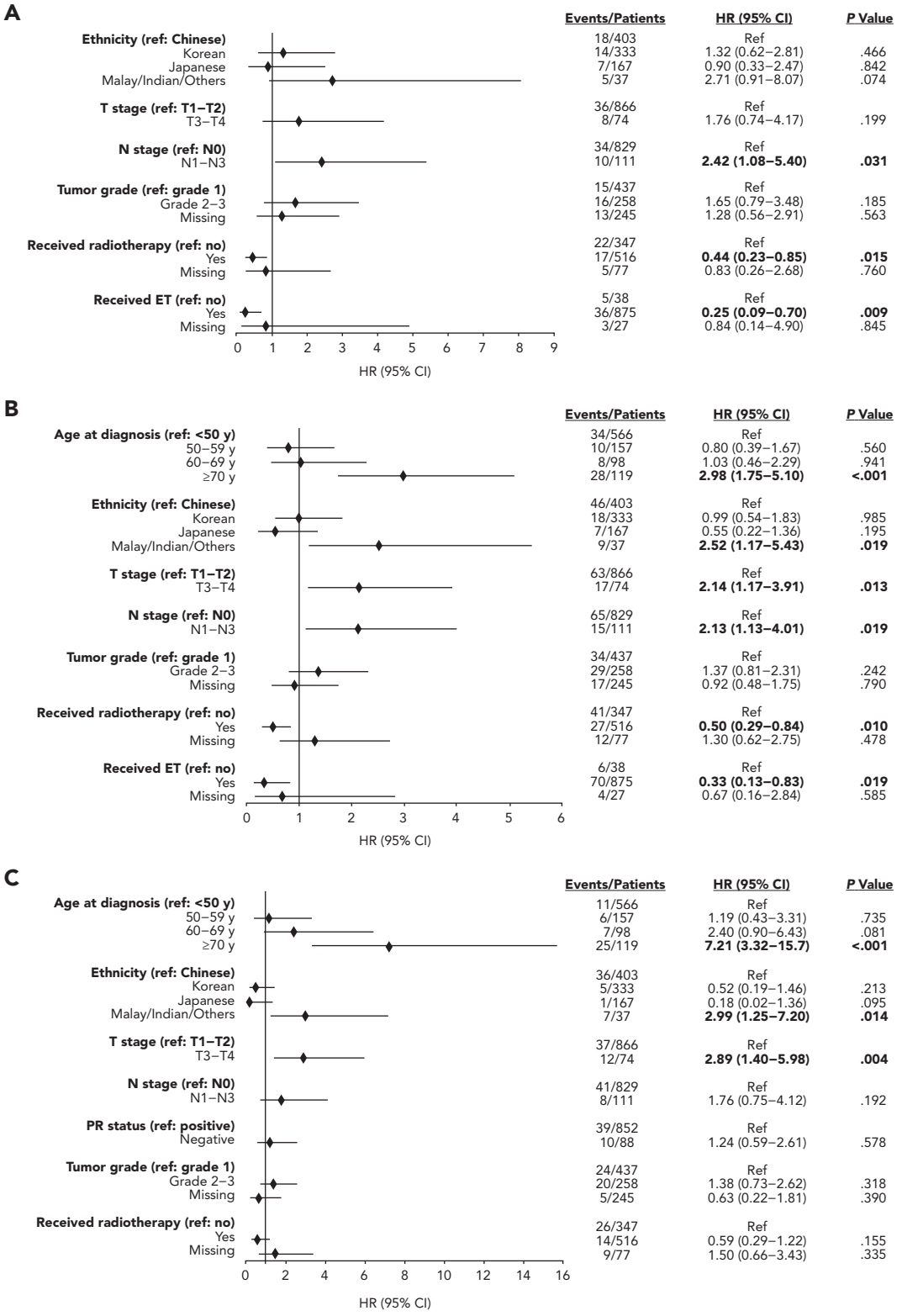

Figure 2. Multivariable Cox regression analysis of **(A)** recurrence-free interval, **(B)** recurrence-free survival, and **(C)** overall survival in PMBC.
Bold indicates statistically significant *P* value.
Abbreviations: ET, endocrine therapy; HR, hazard ratio; PMBC, puremucinous breast cancer; PR, progesterone receptor.

Table 3. Exploratory Subgroup Analysis of Chemotherapy Associations in PMBC Based on the Multicenter Cohort

	RFI			RFS			OS		
	Events/ Patients	HR (95% CI)[a]	P Value[b]	Events/ Patients	HR (95% CI)[a]	P Value[b]	Events/ Patients	HR (95% CI)[a]	P Value[b]
NCCN Guidelines[c] * received chemotherapy			.557[d]			.227[d]			.031[d]
T1–3, N0 or N1mic, tumor size <1 cm: no	5/107	Ref		6/107	Ref		4/107	Ref	
T1–3, N0 or N1mic, tumor size <1 cm: yes[e]	0/7	1.33 (0.06–30.67)	.860	1/7	3.55 (0.55–22.98)	.183	1/7	6.55 (0.86–49.81)	.070
T1–3, N0 or N1mic, tumor size <1 cm: missing[e]	0/5	1.97 (0.09–45.64)	.672	0/5	2.24 (0.11–45.88)	.601	0/5	6.11 (0.26–146.5)	.264
T1–3, N0 or N1mic, tumor size 1 to <3 cm: no	16/406	Ref		24/406	Ref		12/406	Ref	
T1–3, N0 or N1mic, tumor size 1 to <3 cm: yes	3/89	0.92 (0.26–3.26)	.896	6/89	1.40 (0.55–3.52)	.479	3/89	2.33 (0.62–8.70)	.209
T1–3, N0 or N1mic, tumor size 1 to <3 cm: missing[e]	0/11	1.28 (0.06–27.40)	.873	1/11	2.43 (0.43–13.80)	.316	1/11	4.15 (0.66–26.19)	.130
T1–3, N0 or N1mic, tumor size ≥3 cm: no	5/118	Ref		20/118	Ref		17/118	Ref	
T1–3, N0 or N1mic, tumor size ≥3 cm: yes	4/53	1.94 (0.49–7.71)	.348	4/53	0.75 (0.25–2.28)	.614	2/53	1.04 (0.23–4.77)	.962
T1–3, N0 or N1mic, tumor size ≥3 cm: missing[e]	1/5	6.28 (0.89–44.38)	.066	1/5	1.47 (0.26–8.36)	.665	0/5	0.42 (0.02–9.09)	.579
T1–3, N0 or N1mic, missing tumor size: no	0/22	Ref		1/22	Ref		1/22	Ref	
T1–3, N0 or N1mic, missing tumor size: yes[e]	1/9	8.85 (0.28–278.9)	.216	2/9	5.15 (0.62–42.79)	.129	1/9	3.96 (0.35–45.40)	.269
T1–3, N0 or N1mic, missing tumor size: missing[e]	0/11	2.00 (0.03–141.7)	.749	0/11	0.58 (0.02–17.27)	.756	0/11	0.57 (0.02–19.39)	.754
N1 (excl N1mic), N2, N3: no	0/19	Ref		4/19	Ref		4/19	Ref	
N1 (excl N1mic), N2, N3: yes	8/75	4.04 (0.18–91.64)	.381	9/75	0.86 (0.25–2.95)	.806	2/75	0.43 (0.07–2.50)	.346
N1 (excl N1mic), N2, N3: missing[e]	1/3	50.40 (1.53–1,662.4)	.028	1/3	11.97 (1.64–87.38)	.014	1/3	40.82 (4.76–350.0)	.001
Age * received chemotherapy			.653[d]			.531[d]			.107[d]
<50 y: no	15/383	Ref		18/383	Ref		5/383	Ref	
<50 y: yes	11/169	1.44 (0.65–3.17)	.365	15/169	1.51 (0.76–3.00)	.238	5/169	1.67 (0.48–5.78)	.417
<50 y: missing[e]	0/14	1.04 (0.06–19.21)	.979	1/14	1.71 (0.23–12.83)	.604	1/14	6.54 (0.76–56.33)	.088
≥50 y: no				37/289	Ref		33/289	Ref	
≥50 y: yes	11/289	Ref		7/64	0.88 (0.39–1.98)	.758	4/64	0.55 (0.19–1.54)	.254
≥50 y: missing	5/64	2.31 (0.81–6.61)	.118	2/21	0.77 (0.18–3.21)	.717	1/21	0.41 (0.06–3.03)	.382

Abbreviations: excl, excluding; HR, hazard ratio; OS, overall survival; PMBC, pure mucinous breast cancer; RFI, recurrence-free interval; RFS, recurrence-free survival.
[a]Adjusted for age in the NCCN Guidelines subgroup analysis.
[b]Based on Wald's test.
[c]There were 7 patients with T4N0, who were combined with the T1–3 N0 or N1mic patients for analysis.
[d]Interaction between receipt of chemotherapy and subgroup variable.
[e]The small number of PMBCs under this category precludes any firm conclusion.

relapses. Nonetheless, these findings are generally consistent with another recent study based on the SEER database, which also found positive LN status to be a significant independent adverse prognostic factor on Cox multivariable analyses of BCSS for PMBCs.[3] Receipt of adjuvant radiotherapy was also found to be a protective prognostic factor in 3 SEER-based studies.[3,25,26] In our opinion, it is critical to distinguish the type of events when using these commonly used endpoints for evaluating cancer-related outcomes. This was why we analyzed RFI as well, which excludes non-BC deaths and is a more meaningful endpoint in a cancer subtype with better prognosis.

Some observations from our exploratory analyses of systemic therapies are worth mentioning. First, with regard to chemotherapy, we did not find better outcomes with the use of chemotherapy in our multicenter cohort for any patient subgroup defined by age group and by nodal stage and tumor size as per NCCN Guidelines[9] (Table 3). Second, to validate these findings, we analyzed the same subgroups in the SEER database, with further adjustment for additional covariates such as ethnicity, tumor grade, and radiotherapy given the larger number of events and patients in SEER. We found a similar lack of superior outcomes with chemotherapy for these subgroups. Although there was a significant association for superior OS observed with chemotherapy in patients aged >50 years in the SEER cohort, we did not see a superior BCSS in the same subgroup, suggesting that it may have been confounded by other factors unaccounted for in the analyses. Moreover, a significant association for inferior BCSS with chemotherapy was seen in the SEER subgroup of LN-negative tumors ≥3 cm (Table 4).

These findings are similar to a Korean population-based study by Kim et al[10] (n=3,076). Although another, smaller SEER-based propensity score matching analysis by Gao et al[11] (n=805) found an improved OS for adjuvant chemotherapy in patients with LN-positive tumors or tumors ≥3 cm, there was no improved BCSS. In another SEER database study, the frequency of T1–T2N0 ER-positive BCs with high-risk 21-gene Oncotype DX Breast Recurrence Score (>30) was lower in patients with mucinous adenocarcinoma (3.4%) compared with infiltrating ductal

Table 4. Exploratory Subgroup Analysis of Chemotherapy Associations in PMBC Based on SEER Data

	OS			BCSS		
	Events/ Patients	Adjusted HR (95% CI)[a]	*P* Value[b]	Events/ Patients	Adjusted HR (95% CI)[a]	*P* Value[b]
NCCN Guidelines[c] * received chemotherapy			.783[d]			.068[d]
T1–3, N0, or N1mic, tumor size <1 cm: no/unknown	210/1,233	Ref		17/1,233	Ref	
T1–3, N0, or N1mic, tumor size <1 cm: yes	3/35	1.07 (0.37–3.08)	.907	0/35	1.62 (0.09–28.15)	.740
T1–3, N0, or N1mic, tumor size 1 to <3 cm: no/unknown	637/2,882	Ref		77/2,882	Ref	
T1–3, N0, or N1mic, tumor size 1 to <3 cm: yes	14/197	0.86 (0.51–1.47)	.591	5/197	2.33 (0.94–5.76)	.068
T1–3, N0, or N1mic, tumor size ≥3 cm: no/unknown	213/641	Ref		26/641	Ref	
T1–3, N0, or N1mic, tumor size ≥3 cm: yes	15/112	1.07 (0.64–1.81)	.789	10/112	4.94 (2.30–10.57)	<.001
N1 (excl N1mic), N2, N3: no/unknown	53/135	Ref		16/135	Ref	
N1 (excl N1mic), N2, N3: yes	23/179	0.75 (0.46–1.24)	.265	12/179	1.20 (0.55–2.64)	.642
Age at diagnosis * received chemotherapy			.027[d]			.512[d]
<50 y: no/unknown	16/471	Ref		3/471	Ref	
<50 y: yes	9/198	0.93 (0.42–2.09)	.863	5/198	1.59 (0.40–6.32)	.514
≥50 y: no/unknown	1,097/4,420	Ref		133/4,420	Ref	
≥50 y: yes	46/325	0.36 (0.26–0.49)	<.001	22/325	0.98 (0.57–1.71)	.955

Abbreviations: BCSS, breast cancer–specific survival; excl, excluding; HR, hazard ratio; OS, overall survival; PMBC, pure mucinous breast cancer.
[a]Adjusted for age at diagnosis, ethnicity, tumor grade, and receipt of radiotherapy in the NCCN Guideline subgroup analysis, and ethnicity, T stage, N stage, tumor grade, and receipt of radiotherapy in the age subgroup analysis.
[b]Based on Wald's test.
[c]There were 27 patients with T4N0, who were combined with the T1–3 N0 or N1mic patients for analysis.
[d]Interaction between receipt of chemotherapy and subgroup variable.

carcinoma (8.9%). Multivariate prognostic analysis could not be performed for less-frequent histologic subtypes, such as mucinous carcinoma, to test the association of improved BCSS with various factors, such as chemotherapy, due to the low number of BC-specific deaths.[27] To establish the true benefit of treatments, randomized clinical trials on PMBCs are essential but unlikely to be conducted. In the absence of level 1 evidence, cohort studies such as ours provide important insight on the association of specific treatments with cancer outcomes.

Finally, with regard to ET, our exploratory findings largely corroborate with current NCCN Guideline treatment recommendations.[9] Use of ET appeared to be associated with superior outcomes across all subgroups except for LN-negative or N1mic PMBC <1 cm. (Supplementary Table S7). The use of ET is not captured in the SEER database. To our knowledge, these results have not been previously reported in other datasets and will be challenging to replicate given the need to capture relapse events in a large cohort and the widespread use of ET today. These results need to be interpreted with caution given the limitations regarding the small number of patients who did not receive ET and the low event rate with this favorable histology.

The key strengths of this study were the large number of patients and that all participating centers adopted ASCO/CAP guidelines and AJCC TNM staging, which provided a measure of standardization in key patient selection criteria, including HER2, ER, and PR status and overall disease stage. There was also a low level of heterogeneity in all survival outcomes across study centers. Other limitations of this study include its retrospective nature over a long study period and lack of central pathology review as in other large cohort studies of mucinous BC.[1–3] However, all databases were maintained prospectively with capture of events in an unbiased manner. Moreover, histologic classification by reporting pathologists in each database was based on WHO classification of breast tumors, a universally available and referenced resource, for which definitions of ductal, lobular, and mucinous carcinomas have not changed over the study period.[5]

Conclusions

Compared with IDC, PMBC demonstrated superior RFI, RFS, and OS, whereas ILC had similar survival outcomes. Overall, our data support the classification of PMBC as one of the favorable histologies in the current NCCN Guidelines, with de-escalation of treatment recommendations. LN negativity, adjuvant radiotherapy, and ET were associated with superior RFI. However, adjuvant chemotherapy was not associated with better outcomes in exploratory subgroup analyses on patients with node-positive tumors, those with larger tumor size, or those aged <50 years in both our multicenter cohort and our SEER cohort.

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