Treatment Regimens and Survival Outcomes of Primary Neuroendocrine Carcinoma of Breast Compared with Infiltrating Ductal Carcinoma: A Large Propensity Score Matching Study

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Research Article

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Abstract

Purpose

The role of treatment regimens in Neuroendocrine carcinoma of breast (NECB) is not well defined. The aim of this study was to explore the clinical characteristics, treatment regimens and prognosis of NECB compared to infiltrating ductal breast carcinomas(IDCB).

Method

NECB and IDCB patients diagnosed between January 1,2004 and December 12,2016 were enrolled in the researches from the SEER registries. A propensity score matching (PSM) with ratio of 1:5 was performed to correct the selection bias. The Kaplan-Meier curves was used in the analysis of variables. The Cox model was adopted to calculate univariate and multivariate analysis.

Results

Compared to IDCB, NECB patients were elder white females. The NECB group demonstrated a significantly poorer survival compared to IDCB group in both disease-specific survival (DSS) ($p<0.0001$) and overall survival (OS) ($P<0.0001$). In univariate survival analysis, NECB patients were associated with poorer survival compared with IDCB patients. In multivariate survival analysis, earlier T stage, age <60, black race and absence of distant metastasis were independently associated with better DSS and OS after adjusting all variables. In both univariate and multivariate analysis, chemotherapy and surgery were independently associated with better survival.

Conclusion

NECB were a kind of rare and aggressive breast neoplasm with advanced disease stage and pooper prognosis compared to IDCB. Our outcomes supplied sufficient evidence that surgery and chemotherapy contribute to better survival of NECB patients.

Introduction

Neuroendocrine carcinoma of breast (NECB) is a quite rare subtype of neuroendocrine neoplasia accounting for less than 1 % of all cases[1]. Neuroendocrine neoplasm is a heterogeneous kind of tumors which may originate from nearly all organs with endocrine system behavior[2]. About 70% of the neuroendocrine neoplasia occurred in gastroenteric pancreatic system, 25% in the bronchopulmonary system. Relative rare occurs in thyroid gland, skin, bladder and larynx[3].

Initially, NECB was first reported by Feyrter at all in 1963 as a new kind of invasive breast cancer[4]. Then in 1977, Cubilla at all identified eight similar cases and summarized it characteristics[5]. Until 2002, the NECB was firstly defined and in the following year 2003, it was adopted as an individual type of

carcinoma by the World Health Organization (WHO)[6–8]. In previous, the specific markers of NECB were deficient resulting in many NECB patients missed diagnosed in routinely clinical work.

In the WHO Classification of Tumors of the Breast of 2012, the classification of NECB was corrected and categorized as three subgroups:1) well-differentiated neuroendocrine tumors;2) poorly differentiated neuroendocrine carcinoma or small cell carcinoma of breast and 3) invasive breast carcinoma with neuroendocrine differentiation. Among the other type of breast cancers such as invasive ductal, lobular, colloid and papillary carcinoma, the neuroendocrine differentiation can also be observed[9].

No specific therapeutic guidelines for the treatment of NCEB was published and the accessible data mainly derived from case reports and small scale retrospective trials. Most adopted strategies of NECB were referred to conventional breast cancer type. As regarding to the survival of NECB, the view was controversial: some researches indicated that the survival of NECB was poor, while others showed that it was better than infiltrating ductal breast carcinomas(IDCB)[6]. In addition, no significant difference between them was observed in some researches[10].

In this research, we present a propensity score matching (PSM) study with each NECB patients matching five IDCB patients. The aim of this study was to explore the clinical characteristics, treatment regimens and prognosis of NECB compared to infiltrating ductal breast carcinomas (IDCB), for IDCB is the most popular subtye of malignant breast cancer.

Method

Patients

The SEER Program maintained by the US National Cancer Institute (NCI) provided a data source for rare disease which contained 28% population of US, the largest publicly available cancer database[11]. NECB and IDCB patients diagnosed between January 1, 2014 and December 12, 2016 were concluded in the researches. Only primary neoplasm patients with definitely pathologic diagnosis were eligible in the research. The included NECB patients was based on the third edition of the International Classifications of Diseases for Oncology (ICD-O-3) corrected by WHO in 2012. The cases of NEC (ICD-O-3 8013/3, 8041/3, 8246/3 and 8249/3) and breast (ICDO-2 codes, C50.0-50.6, 8, 9) was eligible. The primary site of neoplasm included nipple (C50.0), central portion of breast (C50.1), upper inner quadrant of breast(C50.2), lower inner quadrant of breast (C50.3), upper outer quadrant of breast(C50.4),lower outer quadrant of breast (C50.5),axillary tail of breast (C50.6),overlapping lesion of breast (C50.8) and breast not otherwise specified(NOS)(C50.9).

Clinical Characteristics

Age at diagnosis, sex, race, primary site, marital status, seer stage (regional, localized, distant),TNM stage, molecular subtype (Luminal A, Luminal B, Triple Negative), treatment regimens (surgery, chemotherapy,

radiation) of patients were collected from the SEER database and used to analyze the risk factors of NECB patients. Age were continuous variables and were classified as two categorical variables (< 60 year,≧ 60 year). Before 2015, the tumor stage was coded regarding to American Joint Committee on Cancer(AJCC) tumor, node, metastasis classification staging system,6th edition. From 2016, the category was according to 7th edition.

A PSM was performed between NECB and IDCB patients with 1:5 ratio by each variables including age at diagnosis, sex, race, primary site, marital status, seer stage (regional, localized, distant), TNM stage, molecular subtype (Luminal A, Luminal B, Triple Negative),treatment regimens (surgery, chemotherapy, radiation).

Statistical Analyses

Rates of overall survival (OS) and disease-specific survival (DSS) were considered as endpoints of the survival of patients. OS was measured from the day of diagnosis to the day of death caused by any reasons. DSS was evaluated from the day of diagnosis to the day of death caused by breast carcinoma. The Kaplan-Meier curves method was used in performing the survival analysis of clinical variables. The Cox proportional hazards model was adopted to calculate univariate and multivariate analysis. The outcome of risks of OS and DSS were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). All the statistical analyses and graphics were performed with the SPSS 25.0 software (SPSS Inc, Chicago, Illinois, USA) and R statistical software (version-4.0.2.). P value < 0.05 is considered as statistically significant.

Results

Patients

By researching the SEER database, a total of 698363 malignant mammary carcinoma patients was identified from January 1, 2004 to December 12, 2016. Of which ,426 NECB patients were collected and 295 patients finally enrolled in study. The demographic and clinical characteristics of eligible NECB and IDCB patients were shown in the Table 1 before the PSM. Significant differences were identified between NECB and IDCB patients population with regarding to age at diagnosis, sex, primary site, SEER stage, T stage, N stage, distant metastasis, molecular subtype, rate of surgical method, rate of chemotherapy and rate of radiation. But, there was no significant differences shown in race and marital status. Compared to IDCB patients, NECB patients were more elder (41.7% vs 53.2%, p < 0.0001). NECB patients presented with greater frequency of distant stage than IDCB patients(25.1% vs 5.9%, p < 0.0001). There was more triple negative type in NECB patients than that in IDCB patients(14.9% vs 6.4%, p < 0.001). The proportion of received surgery or radiation was less in NECB compared to those in IDCB, respectively. In contrast, Patients treated with chemotherapy in NECB was more than that in IDCB (52.9% vs 44.2%, p < 0.003).

Table 1
The demographic and clinical characteristics of eligible NECB and IDCB patients before the propensity score-match.

Characteristics	NECB	IDCB	*p*
Age (%)			
≤ 60 years	123(41.7)	223381(53.2)	< 0.001
60 years	172(58.3)	196810(46.8)	
Sex (%)			
Female	289(98.0)	416917(99.2)	0.034
Male	6(2.0)	3274(0.8)	
Race (%)			
Black	43(14.6)	48304(11.5)	0.094
White	231(78.3)	330295(78.6)	
Other/ Unknown	21(7.1)	41592(9.9)	
Primary Site (%)			
Central portion0	10(3.4)	25102(6.0)	< 0.001
Upper-inner	28(9.5)	50008(11.9)	
Lower-inner	11(3.7)	23848(5.7)	
Upper-outer	90(30.5)	143516(34.2)	
Lower-outer	22(7.5)	30287(7.2)	
Overlapping lesion	63(21.4)	92656(22.1)	
Breast,NOS	71(24.1)	54774(13.0)	
Marital status (%)			
Married	230(78.0)	337286(80.3)	0.459
Unmarried	51(17.3)	61856(14.7)	
Unknown	14(4.7)	21049(5.0)	
SEER Stage (%)			
Regional	81(27.5)	127597(30.4)	< 0.001
Localized	134(45.4)	264073(62.8)	
Distant	74(25.1)	24848(5.9)	

Characteristics	NECB	IDCB	*p*
Unknown	6(2.0)	3673(0.9)	
T stage (%)			
T0	1(0.3)	275(0.1)	< 0.001
T1	63(21.4)	242299(57.7)	
T2	104(35.3)	115467(27.5)	
T3	29(9.8)	17477(4.2)	
T4	12(4.1)	11005(2.6)	
Unknown	86(29.2)	33668(8.0)	
N stage (%)			
N0	159(53.9)	266194(63.4)	< 0.001
N1	65(22.0)	96607(23.0)	
N2	12(4.1)	23708(5.6)	
N3	22(7.5)	16677(4.0)	
Unknown	37(12.5)	17005(4.0)	
Metastasis (%)			
M0	215(72.9)	394997(94.0)	< 0.001
M1	66(22.4)	18279(4.4)	
Unknown	14(4.7)	6915(1.6)	
Molecular subtype			
Luminal A	84(28.5)	147791(35.2)	< 0.001
Luminal B	16(5.4)	26341(6.3)	
Triple Negative	44(14.9)	27081(6.4)	
Unknown	151(51.2)	218978(52.1)	
Surgery (%)			
Yes	206(69.8)	389733(92.8)	< 0.001
No/unknown	89(30.2)	30458(7.2)	
Radiation (%)			
Yes	132(44.7)	214740(51.1)	0.033

Characteristics	NECB	IDCB	*p*
No/unknown	163(55.3)	205451(48.9)	
Chemotherapy (%)			
Yes	156(52.9)	185668(44.2)	0.003
No/unknown	139(47.1)	234523(55.8)	

Survival Analysis Of Necb

The rates of OS were decreased in patients not treated with radiation compared with those treated with radiation (1-year 68.6% vs 83.8%,3-year 52.9% vs 68.6%, 5-year 48.9% vs 58.9%) (Fig. 1A and B). The 1-year, 3-year, 5-year rates of OS in patients received chemotherapy was 80.6% ,67.3% and 65.1%, respectively, compared with patients who had not received chemotherapy(1-year 76.2%, 3-year 62.1%, 5-year 55.6%,respectively)(Fig. 1C and D). In the 3-year survival analysis, the rates of DSS of patients undergone surgery were over two times of patients who were not undergone surgery(73.6% vs 34.0%) (Fig. 1E and F). To OS, the rates of patients undergone surgery were nearly three times of patients who were not undergone surgery (73.6% vs 25.7%). The 5- year rates were also with greater difference.

Survival Analysis After Psm

Each NECB patients were matched with five IDCB patients data to gain more sight of baseline demographic and diagnostic differences by all variables as age at diagnosis, sex, race, marital status, primary site, SEER stage, T stage, N stage, distant metastasis, molecular subtype, rate of surgical method, chemotherapy and radiation. After matching, good balance with no significant difference was observed between the NECB and IDCB patients groups(Table 2).

Table 2
The demographic and clinical characteristics of eligible NECB and IDCB patients after the propensity score-match.

Characteristics	NECB	IDCB	*p*
Age (%)			
≤ 60 years	123(41.7)	642(43.5)	0.607
60 years	172(58.3)	833(56.5)	
Sex (%)			
Female	289(98.0)	1454(98.6)	0.603
Male	6(2.0)	21(1.4)	
Race (%)			
Black	43(14.6)	236(16.0)	0.609
White	231(78.3)	1116(75.7)	
Other/ Unknown	21(7.1)	123(8.3)	
Primary Site (%)			
Central portion	10(3.4)	72(4.9)	0.754
Upper-inner	28(9.5)	114(7.7)	
Lower-inner	11(3.7)	68(4.6)	
Upper-outer	90(30.5)	464(31.5)	
Lower-outer	22(7.5)	97(6.6)	
Overlapping lesion	63(21.4)	332(22.5)	
Breast,NOS	71(24.1)	328(22.2)	
Marital status (%)			
Married	230(78.0)	1137(77.1)	0.582
Unmarried	51(17.3)	245(16.6)	
Unknown	14(4.7)	93(6.3)	
SEER Stage (%)			
Regional	81(27.5)	475(32.2)	0.284
Localized	134(45.4)	623(42.2)	
Distant	74(25.1)	333(22.6)	

Characteristics	NECB	IDCB	*p*
Unknown	6(2.0)	44(3.0)	
T stage (%)			
T0	1(0.3)	0(0.0)	0.097
T1	63(21.4)	317(21.5)	
T2	104(35.3)	506(34.3)	
T3	29(9.8)	129(8.7)	
T4	12(4.1)	108(7.3)	
Unknown	86(29.2)	415(28.1)	
N stage (%)			
N0	159(53.9)	739(50.1)	0.609
N1	65(22.0)	374(25.4)	
N2	12(4.1)	79(5.4)	
N3	22(7.5)	109(7.4)	
Unknown	37(12.5)	174(11.8)	
Metastasis (%)			
M0	215(72.9)	1112(75.4)	0.660
M1	66(22.4)	298(20.2)	
Unknown	14(4.7)	65(4.4)	
Molecular subtype			
Luminal A	84(28.5)	442(30.0)	0.679
Luminal B	16(5.4)	90(6.1)	
Triple Negative	44(14.9)	184(12.5)	
Unknown	151(51.2)	759(51.5)	
Surgery (%)			
Yes	206(69.8)	1007(68.3)	0.647
No/unknown	89(30.2)	468(31.7)	
Radiation (%)			
Yes	132(44.7)	585(39.7)	0.119

Characteristics	NECB	IDCB	*p*
No/unknown	163(55.3)	890(60.3)	
Chemotherapy (%)			
Yes	156(52.9)	819(55.5)	0.442
No/unknown	139(47.1)	656(44.5)	

Table 3
Univariate survival analysis (Kaplan-Meier) in subgroups of patients according to characteristics

Parameter	DSS		OS	
	HR (95% CI)	p	HR (95% CI)	p
Age		0.417		0.331
≤ 60 years	1		1	
60 years	1.178(0.793–1.748)		1.186(0.840–1.675)	
Sex		0.745		0.561
Male	1		1	
Female	1.262(0.311–5.123)		1.514(0.374–6.129)	
Race		0.578		0.530
White	1		1	
Black	1.188(0.702–2.008)		1.120(0.700-1.791)	
Other*/Unknown	1.371(0.687–2.735)		1.384(0.761–2.518)	
Primary Location		0.702		0.785
other	1		1	
inner	1.110(0.615–2.003)		1.162(0.689–1.958)	
outer	0.875(0.574–1.334)		0.962(0.667–1.387)	
Marital status		0.179		0.685
Married	1		1	
Unmarried	0.653(0.364–1.172)		0.910(0.579–1.430)	
Unknown	1.472(0.680–3.185)		1.297(0.631–2.664)	
SEER Stage		0.133		0.203
Regional	1		1	
Localized	1.354(0.846–2.164)		1.403(0.922–2.136)	
Distant	0.847(0.476–1.506)		1.012(0.619–1.654)	
Unknown	2.341(0.706–7.763)		2.038(0.622–6.681)	

*Including American Indian/Alaskan native, and Asian/Pacific Islander, and others unspecified.

Parameter	DSS		OS	
T stage		0.045		0.017
Tis-T2	1		1	
T3-T4	0.415(0.199–0.867)		0.423(0.225–0.795)	
Unknown	1.007(0.660–1.537)		1.017(0.703–1.470)	
N stage		0.003		0.002
N0	1		1	
N1-3	0.888(0.569–1.386)		0.798(0.540–1.178)	
Unknown	2.194(1.303–3.694)		1.951(1.222–3.113)	
Metastasis		0.008		0.060
M0	1		1	
M1	0.795(0.485–1.302)		0.897(0.595–1.352)	
Unknown	2.738(1.306–5.742)		2.223(1.069–4.620)	
Molecular subtype		0.842		0.666
Luminal A	1		1	
Luminal B	1.052(0.440–2.512)		1.264(0.641–2.599)	
Triple Negative	0.905(0.498–1.644)		0.884(0.519–1.505)	
Unknown	0.831(0.533–1.294)		0.857(0.581–1.266)	
Surgery		0.000		0.000
No/Unknown	1		1	
Yes	0.241(0.162–0.358)		0.221(0.155–0.314)	
Radiation		0.074		0.025
No/Unknown	1		1	
Yes	0.698(0.471–1.035)		0.674(0.477–0.951)	
Chemotherapy		0.195		0.025
No/Unknown	1		1	
Yes	0.775(0.526–1.140)		0.680(0.485–0.954)	
*Including American Indian/Alaskan native, and Asian/Pacific Islander, and others unspecified.				

The NECB patients demonstrated significantly poorer survival compared to IDCB patients in both DSS ($p < 0.0001$) and OS ($P < 0.0001$)(Fig. 2). Actuarial 1-year, 3-year and 5-year DSS rates were 80.1%, 64.9%, and 60.8% vs. 91.6%, 80.4%, and 71.9%, respectively. The 1-year, 3-year and 5-year actuarial OS for the NECB and IDCB group were 75.5%, 60.9%, and 53.4% vs. 89.2%, 74.0%, and 63.4%, respectively.

Univariate And Multivariate Survival Analysis Of Necb

In univariate survival analysis, advanced T stage, N stage and metastasis status were found that related as to survival of NECB patients(Table 2). Patients received radiation therapy had an estimated 32.6% reduced risk of death of NECB (HR = 0.673, 95%CI,0.477–0.951, p = 0.025). NECB patients treated with chemotherapy had an estimated 32.0% reduced risk of death compared to those who had not received chemotherapy or chemotherapy history unknown (HR = 0.68, 95% CI, 0.477–0.951, p = 0.025). Surgery were demonstrated significantly improved the DSS (HR = 0.241, 95%CI, 0.162–0.358, $p < 0.0001$) and OS (HR = 0.221, 95%CI, 0.155–0.314, $p < 0.0001$)in NECB patients. Age at diagnosis, sex, race, primary tumor location, marital status and SEER stage were not significant risk variables for NECB. As regarding to different molecular subtype, no statistically significant OS and DSS were identified among NECB patients in univariate survival analysis.

In multivariate survival analysis, Tis-T2, age < 60 ,black race and no distant metastasis were independently associated with improved DSS and OS after adjusting all variables(Table 4). Female patients were reported with a better OS (HR = 0.523,95% CI, 0.302–0.907, p = 0.021). Compared to regional SEER stage, localized SEER stage patients were related to better DSS(HR = 0.621, 95% CI,0.437–0.883, p = 0.008). Chemotherapy and surgery served as positive survival factors in the DSS and OS of NECB patients, independently. Interestingly, the multivariate analysis outcomes of Luminal A type and triple negative type were contrast with univariate analysis. Triple negative type patients were correlated with worse DSS (HR = 2.113; 95% CI, 1.555–2.908, $p < 0.0001$) and OS (HR = 1.974; 95% CI, 1.496–2.606, $p < 0.0001$).

Table 4
Multivariate analysis of disease-specific survival (DSS) and overall survival (OS) predictors using Cox proportional hazard model

Parameter	DSS		OS	
	HR (95% CI)	p	HR (95% CI)	p
Age(≧ 60 years)	1.336(1.102–1.619)	0.003	1.678(1.422–1.980)	0.000
Sex (Female)	1.009(0.404–2.524)	0.984	0.523(0.302–0.907)	0.021
Race				
Black vs. White	1.519(1.198–1.925)	0.001	1.431(1.169–1.752)	0.001
Other*/Unknown vs. White	0.657(0.440–0.981)	0.040	0.713(0.511–0.994)	0.046
Primary Location				
Upper-inner vs. Central portion	1.360(0.793–2.332)	0.263	1.148(0.740–1.779)	0.539
Lower-inner vs. Central portion	0.842(0.438–1.621)	0.607	0.884(0.518–1.507)	0.650
Upper-outer vs. Central portion	0.854(0.534–1.336)	0.510	0.912(0.624–1.332)	0.633
Lower-outer vs. Central portion	0.966(0.542–1.722)	0.908	1.045(0.659–1.656)	0.853
Overlapping lesion vs. Central portion	1.193(0.745–1.908)	0.463	1.143(0.783–1.668)	0.488
Breast,NOS vs. Central portion	1.138(0.716–1.808)	0.585	1.097(0.754–1.598)	0.628
Marital status				
Unmarried vs. Married	1.071(0.838–1.369)	0.583	1.153(0.937–1.420)	0.179
Unknown vs. Married	0.498(0.299–0.830)	0.007	0.700(0.477–1.027)	0.068
SEER Stage				
Localized vs. Regional	0.621(0.437–0.883)	0.008	0.849(0.636–1.133)	0.267

*Including American Indian/Alaskan native, and Asian/Pacific Islander, and others unspecified.

Parameter	DSS		OS	
Distant vs. Regional	0.997(0.522–1.906)	0.994	1.129(0.668–1.909)	0.650
Unknown vs. Regional	0.850(0.397–1.817)	0.675	0.966(0.531–1.757)	0.909
T stage				
T3-T4 vs. Tis-T2	1.507(1.112–2.042)	0.008	1.436(1.123–1.836)	0.004
Unknown vs. Tis-T2	0.827(0.380–1.803)	0.633	1.046(0.617–1.773)	0.868
N stage				
N1-3 vs. N0	1.085(0.828–1.422)	0.555	1.052(0.827–1.338)	0.682
Unknown vs. N0	1.161(0.804–1.677)	0.426	1.255(0.904–1.742)	0.175
Metastasis				
M1 vs. M0	4.396(1.671–11.562)	0.003	2.412(1.186–4.903)	0.015
Unknown vs. M0	2.317(1.050–5.116)	0.038	1.103(0.636–1.913)	0.726
Molecular subtype				
Luminal B vs. Luminal A	0.695(0.419–1.153)	0.159	1.102(0.748–1.624)	0.624
Triple Negative vs. Luminal A	2.113(1.555–2.908)	0.000	1.974(1.496–2.606)	0.000
Unknown vs. Luminal A	1.254(0.983–1.599)	0.068	1.311(1.069–1.607)	0.009
Surgery (Yes)	0.405(0.331–0.495)	0.000	0.381(0.322–0.450)	0.000
Radiation (Yes)	0.894(0.725–1.102)	0.292	0.862(0.723–1.028)	0.098
Chemotherapy (Yes)	0.793(0.649–0.970)	0.024	0.660(0.559–0.780)	0.000
Pathological group (IDC)	0.706(0.562–0.887)	0.003	0.741(0.608–0.902)	0.003
*Including American Indian/Alaskan native, and Asian/Pacific Islander, and others				
unspecified.				

Discussion

NECB is a very rare and aggressive subtype of malignant breast neoplasm with few respective clinical trials published[12–14]. The evidence for risk factors and treatment regimens were insufficient. Our studies is the first and largest research to compare the NECB and IDCB by performing PSM to identify treatment regimens and clinical characteristics of NCEB. The current study demonstrated that NECB usually presents in white female population elder than 60, with advanced TNM stage. As previous studies reported, elder patients (> 60) were at a higher risk of NECB comparing to IDCB. In this research, it was shown that the advanced T stage and metastasis status were correlated with worse prognosis in NECB patients as expected. Chemotherapy and surgery could significantly improve the survival of NECB patients. Compared to IDCB patients, NECB patients were with poorer DSS and OS. Reference to molecular subtype, the proportion of luminal A type was the largest of all, followed by triple negative and luminal B type similar to the previous studies. The evidence for risk factors and treatment regimens were insufficient.

The prognosis of NECB versus usual type IDCB had been reported by several studies[15, 16]. Some researchers showed that there was a significant difference between the two subtype. However, some considered that they had similar prognosis[16]. In this research, before matching, patients with NECB tend to be elder, at advance T stage, various proportion of molecular subtype and received different treatment regimens compared to IDCB groups. After matching, survival of NECB was significant worse than IDCB.

Estrogen receptor(ER) and/or progesterone receptor(PR) is positive in majority of NECB patients with the proportion of 68%, while, Her2 is usually negative[17]. Then the patients were subdivided as Luminal A and Luminal B through Ki-67 immunohistochemical staining(15%)[18, 19]. The distribution of luminal A and B was equal identified by some studies. However, some studies discovered that the proportions of luminal A was larger than luminal B. And in some studies, luminal B type counting more[20, 21]. Very rarely triple negative were observed[22]. In our research, the outcomes supported that luminal A type take the largest account of all, followed by triple negative and then luminal B type. Compared to IDCB,more proportion of NECB fall into triple negative group.

Regarding to the high grade malignancy and poor prognosis, efficient treatment is essential to NECB[23–25]. However, there was still no standard treatment for various stage NECB. Surgery is the first choice in treating breast neoplasm[25]. As for general malignant mammary carcinoma,tumor size, the age, tumor site and size, ECOG score status or PS score, patients' willingness, lymph node metastasis and the tolerance were all taken into consideration of before deciding surgery. The surgical procedure conclude lumpectomy, total or modified radical mastectomy and breast reconstruction. In the first respective study of NECB based on SEER, the study cohort was limited to large cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma[26]. Their study suggested that surgery improved the DSS of patients. In another similar studies also based on SEER database, surgery was not considered as an independent

factors in improving survival[8]. The method that surgery improved DSS and OS was approved by our results. The similar trend was also observed in other case series and small sample respective studies[15].

The adjuvant therapy method were based on the biological feature of NECB such as pathological type, lymph node and distant metastasis[27]. Compare to surgery, chemotherapy was also an essential treatment strategies in improving the survival of NECB[22]. However, the effect of chemotherapy was controversial in previous studies. Some researchers did not consider that patients benefit from chemotherapy. They found that the DSS and OS were decreased because of the drug resistance caused by chemotherapy[28]. Some articles demonstrated that chemotherapy decreased the 12% risk of recurrence in ten years[29]. Our outcomes supported that chemotherapy was significant improved the survival of NECB patients. For breast carcinoma, received radiation therapy was an important method in improving survival[30]. The survival analysis showed that radiation was inefficient in prolonging the survival. There was no significant difference between the patients received radiation and those not treated with radiation. Similar results were published in previous studies[27].

Besides the traditional treatment strategies, there was specific regimens in treating neuroendocrine carcinoma, adjuvant endocrine therapy[31, 32]. Patients with hormone receptor-positive were candidates to treat with adjuvant endocrine therapy[32–34]. Particularly, it was quite suitable for elder,not tolerance surgery or chemotherapy patients[35–37]. But some patients rejected to receive endocrine treatment for lacking established procedure or guidelines in NECB. The treatment effect of endocrine therapy was also conflict. It was reported that anti-hormone therapy significant prolonged the OS and disease free survival while some other reports did not approved the results[33, 38]. The efficient of endocrine therapy need further explore. To triple negative patients, hormone therapy was insufficient. And these patients were correlated with poor prognosis[39, 40]. The proportion of triple negative group in NECB patients was larger than IDCB, which is a potential results in explaining relative poor prognosis of NECB.

There were several limitations in our research. Firstly, the detail treatment of patients not provided in the SEER database, making it was impossible to analysis the surgical method, chemotherapy regimens, radiotherapy dose and hormone receptors. It was hardly to analysis the combination treatment effect. Secondly, selection bias may exist in the study for some subgroups just included in limitation sample size patients.

Conclusions

Our study is a large sample, PSM research comparing the demographic and clinical characteristics and risk factors of survival of NECB and IDCB. The analysis showed that NECB patients had advanced SEER stage, more advanced T stage, larger proportion of lymph node metastasis and distant metastasis, and worse OS and DSS compared to IDCB patients. To molecular subtype, NECB tends to be luminal A group. Surgery and chemotherapy, respectively, significantly improved the survival of NECB patients.

Declarations

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Conflict of Interest Statement: All authors declared no conflict of interest.

Availability of data and material All the relative data and material were available

Authors' Contribution Conception and design: QFL, YWZ and XLM collected and assembly of data; YNZ and QFL do the data analysis and interpretation; QFL and YWZ write the manuscript.

Consent to participate All the author approve

Consent for publication All the author approve

Ethical approval: The Ethics Administration Office of West China Hospital, Sichuan University approved our studies. Informed consents were approved waiver by the Ethics Administration Office of West China Hospital. The data agreement was obtained and we downloaded the database directly from the SEER website in keeping with SEER requirements.

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Figures

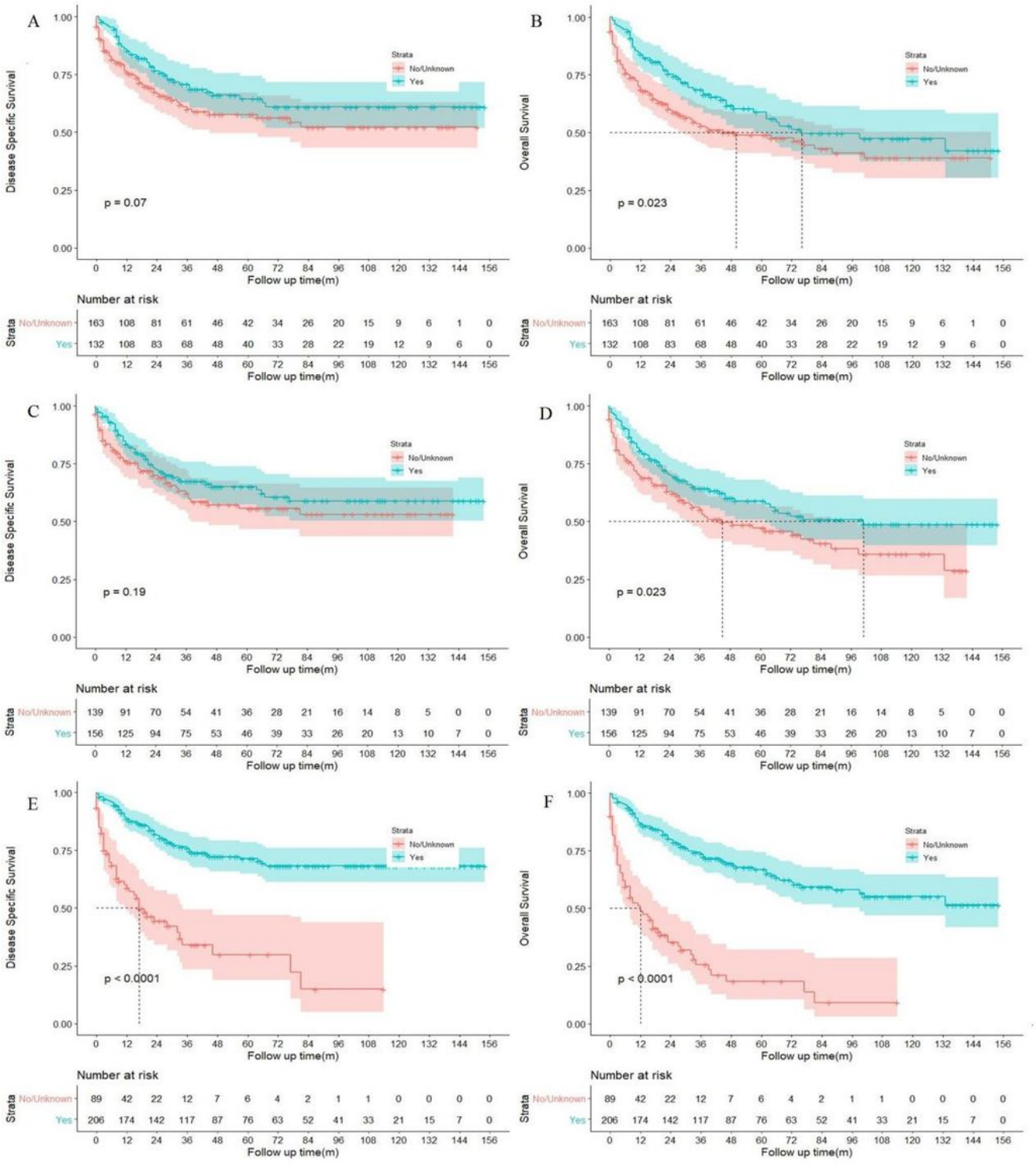

Figure 1

Kaplan-Meier curves of DSS and OS in carcinosacroma of bladder patients according to radiation(A and B),chemotherapy(C and D) and surgery(E and F)

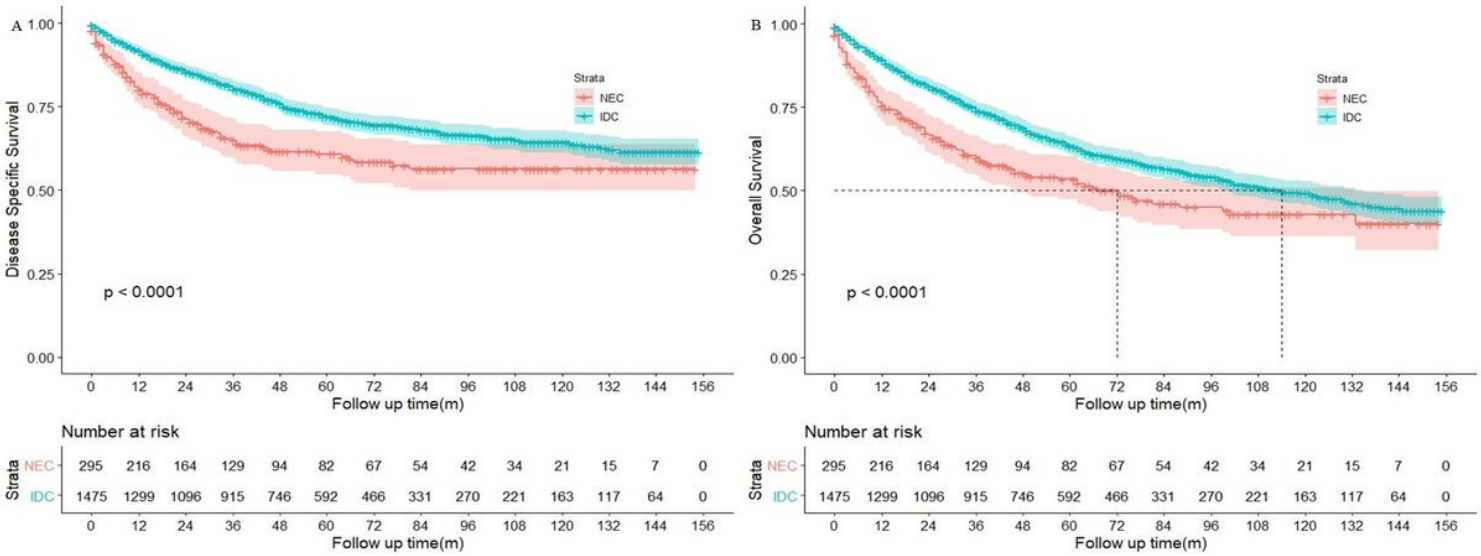

Figure 2

Kaplan-Meier curves of (A) DSS and (B) OS in patients