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ORIGINAL RESEARCH

Clinical Outcomes of N3 Breast Cancer: A Real-World Study of a Single Institution and the US Surveillance, Epidemiology, and End Results (SEER) Database

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Background: Although stage IIIC (any TN3M0) breast cancer is known to have a dismal prognosis, the clinical outcome of current standard management and the prognostic differences between N3a, N3b and N3c remain to be further investigated.

Material and Methods: Data from our center on pathologic N3 (pN3) (n=284) breast cancer and the US Surveillance, Epidemiology, and End Results (SEER) database on clinical N3 (cN3) (n=15,291) and M1 (n=23,623) breast cancer between January 2004 and December 2015 were systematically analyzed for clinicopathological characteristics and survival outcomes.

Results: In our institution, patients with pN3c had the worst survival, with 5-year OS and DFS rates of 52.4% and 41.5%, respectively. Patients with pN3b had a relatively good prognosis, with a 5-year OS rate of 75.3% vs 63.9% for the pN3a group (p=0.045). For DFS, the 5-year survival rate was 63.1% in the pN3b group compared with 40.3% in the pN3a group (p=0.030). In the US SEER database, patients with cN3c had the worst survival in the cN3 group, but the prognosis of cN3c was much better than that of M1. Similarly, patients with cN3b had a better prognosis compared with patients in other groups, with a 5-year OS rate of 68.9% vs 61.9% for the cN3a group (p<0.001) and a 5-year BCSS rate of 73.4% vs 67.1% for the cN3a group (p<0.001).

Conclusion: Breast cancer patients with N3c had the worst clinical outcomes, while the prognosis of N3b patients was better than that of N3a patients.

Keywords: breast cancer, N3, stage IIIC, survival

Background

According to the American Joint Committee on Cancer (AJCC) TNM staging system, N3 breast cancer is divided into N3a, N3b, and N3c on the basis of the specific situation of lymph node metastasis and corresponding prognosis.[1] Patients with stage IIIC disease are considered to have nodal status N3 (cN3a, metastases in ipsilateral infraclavicular lymph node(s) (ICLN(s)); cN3b, metastases in ipsilateral internal mammary lymph node(s) (IMLN(s)) and axillary lymph node(s) (ALN(s)); cN3c, metastases in ipsilateral supraclavicular lymph node(s) (SCLN(s)) (ipsilateral SCLN metastasis; ISLM); pN3a, metastases in 10 or more ALNs or in ICLNs; pN3b, metastases in clinically detected ipsilateral IMLNs in the presence of one or more positive ALNs or in more than 3 ALNs and in IMLNs with micrometastases

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or macrometastases detected by sentinel lymph node biopsy but not clinically detected; pN3c, ISLM, regardless of tumor size (T stage)). According to the 7th version of AJCC,[2] the TNM stage was directly adopted in the ypN stage, although its prognostic significance was not the same.

Stage IIIC breast cancer is also defined as locally advanced breast cancer (LABC), which predicts an unfavorable prognosis compared to those at earlier stages.[3] Over the last decade, the prognosis of advanced breast cancer, such as stage IIIC, has improved as a result of the development of multimodality treatment (including neoadjuvant chemotherapy (NAC), radical surgery, adjuvant chemotherapy, radiotherapy, endocrine therapy, and target therapy).[4–6] According to previous studies, the 5-year DFS and OS rates of N3a, N3b and N3c were approximately 43–66% and 58–81%,[7–12] 56–90% and 71–80%,[13–18] and 25–51% and 33–78%,[17–23] respectively. However, the clinical outcomes under current standard systemic management in a large consecutive sample of N3 breast cancer cases remain unclear to date, and comparative studies on the N3 subgroup are also scarce.

The purpose of this study was to identify the clinical outcome of N3 breast cancer under current standard management and the prognostic differences among N3a, N3b, and N3c from both the cN3 and pN3 aspects.

Materials and Methods

Study Population

The data for this study was obtained from our institution and the Surveillance, Epidemiology, and End Results (SEER) registry. The SEER Program has been collecting data on cancer incidence and mortality from various locations throughout the US since 1973 from 18 population-based registries that represent approximately 30% of the US population. We obtained data from the SEER database by using SEER*Stat software version 8.3.5. This analysis included pathologic N3 (pN3) breast cancer cases from our institution and clinical N3 (cN3) and M1 breast cancer cases reported from the SEER Program diagnosed between 2004 and 2015.

Case Ascertainment

Cohort 1: A total of 352 pN3 cases were diagnosed at the Breast Disease Center, Southwest Hospital, The Army Medical University between 2004 and 2015. We excluded cases that were not primary breast cancer (n = 13), cases with distant metastasis (n = 34), and those who were missing complete clinicopathological and survival data (n = 21), leaving 284 pN3 cases in the analysis.

The US SEER Program data were extracted using SEER*Stat's client-server mode. We used International Classification of Diseases for Oncology, 3rd edition histology and behavior codes (ICD-O-3 morphology code 8500–8599) to identify patients. Cohort 2: A total of 19,371 cN3 cases were diagnosed in the US SEER population from 2004 to 2015. We excluded male cases (n = 359), cases of unknown diagnostic confirmation (n = 68), cases with a different histologic type (other than ICD-O-3 morphology code 8500–8599; n = 592), cases without cancer-directed surgery (n = 177), cases that were not primary tumor (n = 2357), and cases with incomplete survival data and follow-up information (n=527), leaving 15,291 cN3 cases from SEER in the analysis. Cohort 3: A total of 56,504 M1 cases were diagnosed in the US SEER population from 2004 to 2015. We excluded male cases (n = 607), cases of unknown diagnostic confirmation (n = 2461), cases with a different histologic type (other than ICD-O-3 morphology code 8500–8599; n = 5059), cases that were not primary tumor (n = 5008), and cases with incomplete survival data and follow-up information (n=19,746), leaving 23,623 M1 cases from SEER in the analysis (Figure 1).

Study Variables

The primary outcome of interest was survival. Disease-free survival (DFS) was defined as the time from the date of diagnosis to relapse or death. Overall survival (OS) was defined as the time from the date of diagnosis to death from any cause. Breast cancer-specific survival (BCSS) was defined as the time from the date of diagnosis to death from breast cancer.

For cohort 1, we evaluated clinicopathological variables for each case, including age, tumor location (left or right, central, lateral or inner), T stage (6th AJCC TNM stage standard), histological type, estrogen receptor status (ER, positive defined as >1%), progesterone receptor status (PR, positive defined as >1%), Ki-67 labeling index, HER2 status, molecular subtype, the mean number of involved ALNs and number of involved ALNs. ER and PR status, Ki-67 labeling index, and HER2 status were evaluated immunohistochemically, and fluorescence in situ hybridization (FISH) for HER2 status was performed if necessary. Regarding the molecular subtype, patients were classified into three subtype groups: luminal (ER positive and/or PR positive); HER2 (ER

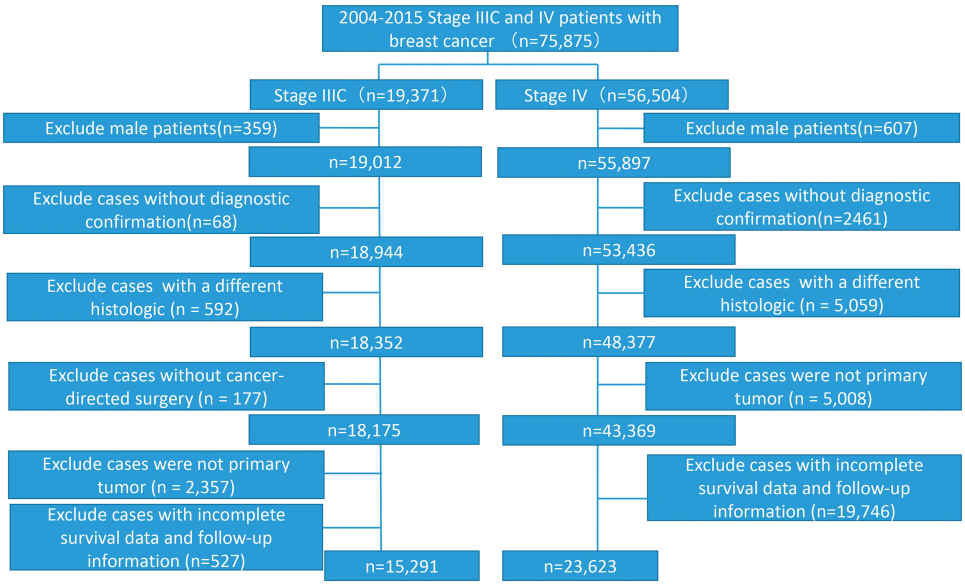


Figure 1 Diagram of Study Cohort From Surveillance, Epidemiology, and End Results (SEER) Database.

negative, PR negative, and HER2 positive); and triple negative (ER negative, PR negative, and HER2 negative).

For cohort 2 and cohort 3, we evaluated independent demographic and clinicopathological variables for each case, including age, race (white, black, and Hispanic/other/unknown), tumor location (classified as central/nipple-areolar complex or by quadrant), histological type, histologic grade (grade 1, 2, 3, and 4), TNM stage (adjusted AJCC 6th T, N, and stage), ER (positive defined as >1%) and PR (positive defined as >1%) status, HER2/neu status, molecular subtype (Her2-/hormone receptor (HR)+, Her2+/HR+, Her2+/HR-, and triple negative), mean number of involved ALNs, the number of involved ALNs (0, 1–3, 4–9, and ≥10), type of surgery (partial mastectomy or mastectomy), radiotherapy, and chemotherapy.

Treatment

The treatments of cohort 1 patients were completed in our center.

Chemotherapy: The median of 4cycles of anthracycline-based NAC was performed. The dose recommended by the National Comprehensive Cancer Network (NCCN) guidelines was used as the starting dose of NAC, and the protocol was adjusted according to the patient's specific situation. Adjuvant chemotherapy was completed after surgery.

Surgery: All patients received modified radical mastectomy after NAC, and ALN dissection of levels I, II, and III was performed. If the results of the ultrasonographic/PET-CT report showed suspicious lymph nodes in the internal mammary and supraclavicular regions, then IMLN/SCLN dissection/biopsy was performed.

Radiotherapy: The postoperative regional radiotherapy area included the chest wall, the infraclavicular region, the supraclavicular region, the internal mammary region, and the axilla. The dose was 46–50 Gy in 23–25 fractions.

Adjuvant Treatments: Endocrine therapy and trastuzumab therapy (Herceptin) were administered following the rules and protocols of the NCCN guidelines.

Information on the treatments of cohort 2 and cohort 3 patients were obtained from the treatment records of the SEER database.

Statistical Analysis

For clinicopathological data, continuous variables such as age were compared using Student's *t*-test, categorical variables were compared using Pearson's chi-square test and grade variables were compared by nonparametric tests. Survival curves for time-to-event variables were estimated using the Kaplan-Meier method and compared using the Log rank test. Statistical significance was set as a two-sided $p < 0.05$, and all confidence intervals (CI) are stated at the 95% confidence level. All statistical analyses were performed using SPSS statistical software, version 25.0 (IBM Corp, Armonk, NY).

Results

In total, cohort 1 consisted of 284 women who had pN3 breast cancer, cohort 2 contained 15,291 women who had cN3 breast cancer, and cohort 3 consisted of 23,623 women who had M1 breast cancer.

Clinicopathological Characteristics

The demographics and clinicopathological characteristics of the three cohorts are summarized in Tables 1,2 and 3.

In cohort 1, the numbers of pN3a, pN3b, and pN3c patients were 196, 35 and 53, respectively. pN3b patients tended to have a higher proportion of inner quadrant primary tumors than pN3a or pN3c patients (p=0.087). Additionally, pN3b patients were more likely to have invasive lobular carcinoma than pN3a or pN3c patients (p=0.009) and a lower ratio of ≥10 involved ALNs (p=0.008). However, pN3c patients had a higher proportion of Ki-67 ≥14% (p<0.001) and a higher mean number of involved ALNs (p=0.056). (Table 1)

In cohort 2, the numbers of cN3a, cN3b, and cN3c patients were 11,844, 1404 and 891, respectively. All measured variables were significantly different. cN3a patients presented with a higher mean number of involved ALNs (p<0.001) and a higher ratio of ≥10 involved ALNs (p<0.001). cN3b patients had a higher proportion of primary tumors in the inner quadrant (p<0.001). cN3c showed more aggressive clinicopathological characteristics, accompanied by a higher ratio of T4 tumors (p<0.001), a higher proportion of grade III and IV tumors (p<0.001), a higher ER-negative ratio (p<0.001) and a higher PR negative ratio (p<0.001). (Table 2)

In cohort 3, the number of M1patients were 23,623 and the clinicopathological characteristics were summarized in Table 3.

Survival Outcomes

Kaplan–Meier Analyses for pN3 Survival

In cohort 1, the median length of follow-up was 54 months (6–146 months) for the whole pN3 group.

Kaplan-Meier curves comparing the OS and DFS among the groups are presented in Figure 2A–D and Figure 3A–D, respectively. For the whole pN3 group, the 3-year OS and DFS rates were 73.2% and 55.6%, and the 5-year OS and DFS rates were 64.0% and 42.4%, respectively. Patients with pN3c had the worst survival, with a 3-year (5-year) OS of 59.0% (52.4%) and 3-year (5-year) DFS of 45.0% (41.5%). Significantly, patients with pN3b had a relatively good prognosis, with a 3-year (5-year) OS of 82.1% (75.3%) vs 75% (63.9%) for the pN3a group (p=0.045). For DFS, the 3-year and 5-year survival rates were 78.9% and 63.1% in the pN3b group and 54.6% and 40.3% in the pN3a group (p=0.030), respectively.

Kaplan–Meier Analyses for cN3 and M1 Survival

In cohort 2, the median length of follow-up was 49 months (2–155 months) for the whole cN3 group.

Kaplan-Meier curves comparing the OS and BCSS among the groups are presented in Figure 4A–E and Figure 5A–E, respectively. The 3-year OS and BCSS rates were 75.5% and 78.8%, and the 5-year OS and BCSS rates were 61.7% and 66.8%, respectively, for the whole cN3 group. In the cN3 group, patients with cN3c had the worst survival, but the prognosis of cN3c was much better than that of M1, with a 3-year (5-year) OS of 64.9% (49.9%) vs 40.7% (24.6%) for the M1 group (p<0.001) and a 3-year (5-year) BCSS of 67.6% (53.8%) vs 43.8% (27.8%) for the M1 group (p<0.001). Patients with cN3b had a better prognosis compared with patients in other groups, with a 3-year (5-year) OS of 79.4% (68.9%) vs 75.8% (61.9%) for the cN3a group (p<0.001) and a 3-year (5-year) BCSS of 82.5% (73.4%) vs 79.2% (67.1%) for the cN3a group (p<0.001).

Discussion

In 2002, the AJCC made important modifications to the TNM classification of breast cancer in the 6th edition staging system.[24] One of the important changes was that N staging was divided into three groups according to the number of metastatic ALNs and the metastatic status of ICLNs, IMLNs, and SCLNs. Another important modification was that the AJCC 6th edition reclassified ISLM as N3c disease, which was classified as M1 in previous versions. As a result of this modification, the new stage IIIC (any TN3M0), which did not exist in the former AJCC versions, constituted the worst prognostic group in primary breast carcinoma without distant metastasis. TNM staging was further refined in the subsequent AJCC 7th and most recent 8th edition,[1,2] but no major changes in the N stage were made. However, according to the 7th version of AJCC, the TNM stage was directly adopted in the ypN

Table 1 Clinicopathological Characteristics of pN3 Patients

Characteristics	pN3a (%)	pN3b (%)	pN3c (%)	pN3(%)	p value
Number of patients	**196**	**35**	**53**	**284**	
Mean age(years)	46.0±9.2	46.1±8.2	47.6±9.0	46.3±9.1	0.630
Age(years)					0.945
≤35	21(10.7)	5(14.3)	6(11.3)	32(11.3)	
>35	175(89.3)	30(85.7)	47(88.7)	252(88.7)	
Tumor location					0.532
Left	104(53.1)	23(65.7)	27(50.9)	154(54.2)	
Right	92(46.9)	12(34.3)	26(49.1)	130(45.8)	
Tumor quadrant					0.087
Lateral	117(59.7)	17(48.6)	37(69.8)	175(61.6)	
Inner	24(12.2)	10(28.6)	6(11.3)	36(12.7)	
Central	55(28.1)	8(22.9)	10(18.9)	73(25.7)	
Primary tumor size					0.286
T1	14(7.1)	7(20.0)	6(11.3)	27(9.5)	
T2	109(55.6)	16(45.7)	34(64.2)	159(56.0)	
T3	59(30.1)	12(34.3)	8(15.1)	79(27.8)	
T4	14(7.1)	0(0)	5(9.4)	19(6.7)	
Histological type					0.009
Invasive ductal carcinoma	174(88.8)	30(85.7)	42(79.2)	246(86.6)	
Invasive lobular carcinoma	8(4.1)	4(11.4)	3(5.7)	12(4.2)	
Other types	14(7.1)	1(2.9)	8(15.1)	26(9.2)	
ER					0.469
Negative	60(30.6)	15(42.9)	20(37.7)	95(33.5)	
Positive	136(69.4)	20(57.1)	33(62.3)	189(66.5)	
PR					0.651
Negative	74(37.8)	13(37.1)	25(47.2)	112(39.4)	
Positive	122(62.2)	22(62.9)	28(52.8)	172(60.6)	
HER-2					0.687
Negative	151(77.0)	28(80.0)	41(77.4)	220(77.5)	
Positive	37(18.9)	7(20.0)	12(22.6)	56(19.7)	
Unknown	8(4.1)	0(0)	0(0)	8(2.8)	
Ki67					<0.001
≤14%	61(31.1)	15(42.9)	12(22.6)	88(31.0)	
>14%	64(32.7)	10(28.6)	41(77.4)	115(40.5)	
Unknown	71(36.2)	10(28.6)	0(0)	81(28.5)	
Molecular subtype					0.962
Luminal	141(71.9)	24(68.6)	35(66.0)	200(70.4)	
HER2-overexpressing	20(10.2)	5(14.3)	5(9.4)	30(10.6)	
TNBC	33(16.8)	6(17.1)	13(24.5)	52(18.3)	
Unknown	2(1.0)	0(0)	0(0)	2(0.7)	
Mean number of involved ALN	12.4±6.7	10.2±8.1	17.0±13.7	13.0±8.8	0.056
The number of involved ALN					0.008
0	0(0)	0(0)	2(3.8)	2(0.7)	
1–3	11(5.6)	11(31.4)	7(13.2)	29(10.2)	
4–9	49(25.0)	8(22.9)	11(20.8)	68(23.9)	
≥10	136(69.4)	16(45.7)	33(62.3)	185(65.1)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; TNBC, triple negative breast cancer; ALN, axillary lymph node.

Table 2 Clinicopathological Characteristics of cN3 Patients

Characteristics	cN3a (%)	cN3b (%)	cN3c (%)	cN3 (%)	p value
Number of patients	**11,844**	**1404**	**891**	**15,291**	
Race					<0.001
White	9324(78.7)	1031(73.4)	642(72.1)	11,853(77.5)	
Black	1524(12.9)	243(17.3)	175(19.6)	2116(13.8)	
Other/Unknown	959(8.4)	130(9.3)	74(8.3)	1322(8.7)	
Mean age(years)	58.2±13.6	54.1±13.6	55.2±13.6	57.6±13.7	<0.001
Age(years)					<0.001
≤35	446(3.8)	110(7.8)	59(6.6)	669(4.4)	
>35	11,398(96.2)	1294(92.2)	832(93.4)	14,622(95.6)	
Tumor location					0.002
Left	5816(49.1)	724(51.6)	503(56.5)	7614(49.8)	
Right	6023(50.9)	679(48.4)	387(43.4)	7669(50.2)	
Unknown	5(0.0)	1(0.1)	1(0.1)	8(0.1)	
Tumor quadrant					<0.001
Central	910(7.7)	95(6.8)	56(6.3)	1141(7.5)	
Upper-inner	668(5.6)	112(8.0)	48(5.4)	886(5.8)	
Lower-inner	354(3.0)	75(5.3)	35(3.9)	494(3.2)	
Upper-outer	4050(34.2)	400(28.5)	313(35.1)	5157(33.7)	
Lower-outer	772(6.5)	75(5.3)	41(4.6)	957(6.3)	
Overlapping	2552(21.5)	359(25.6)	176(19.8)	3336(21.8)	
Unknown	2538(21.4)	288(20.5)	222(24.9)	3320(21.7)	
Primary tumor size					<0.001
T0/Tis	32(0.3)	3(0.2)	8(0.9)	46(0.3)	
T1	1831(15.5)	206(14.7)	108(12.1)	2312(15.1)	
T2	5390(45.5)	563(40.1)	283(31.8)	6686(43.7)	
T3	2902(24.5)	309(22.0)	164(18.4)	3623(23.7)	
T4	1531(12.9)	303(21.6)	294(33.0)	2385(15.6)	
TX	158(1.3)	20(1.4)	34(3.8)	239(1.6)	
Histological type					<0.001
Ductal	7944(67.1)	1100(78.3)	703(78.9)	10,529(68.9)	
Lobular	2008(17.0)	102(7.3)	55(6.2)	2326(15.2)	
Mixed	1428(12.1)	132(9.4)	63(7.1)	1777(11.6)	
Other	464(3.9)	70(5.0)	70(7.9)	659(4.3)	
Grade					<0.001
I	790(6.7)	57(4.1)	22(2.5)	929(6.1)	
II	4255(35.9)	401(28.6)	209(23.5)	5235(34.2)	
III	6174(52.1)	866(61.7)	574(64.4)	8240(53.9)	
IV	127(1.1)	12(0.9)	14(1.6)	171(1.1)	
Unknown	498(4.2)	68(4.8)	72(8.1)	716(4.7)	
ER					<0.001
Negative	2955(24.9)	543(38.7)	425(47.7)	10,626(69.5)	
Positive	8577(72.4)	844(60.1)	444(49.8)	4278(28.0)	
Borderline/Unknown	312(2.6)	17(1.2)	22(2.5)	387(2.5)	
PR					<0.001
Negative	4458(37.6)	721(51.4)	539(60.5)	8596(56.2)	
Positive	6989(59.0)	652(46.4)	334(37.5)	6199(40.5)	
Borderline/Unknown	397(3.4)	31(2.2)	18(2.0)	496(3.2)	

(*Continued*)

Table 2 (Continued).

Characteristics	cN3a (%)	cN3b (%)	cN3c (%)	cN3 (%)	p value
Number of patients	**11,844**	**1404**	**891**	**15,291**	
HER-2					<0.001
Negative	4319(36.5)	589(42.0)	291(32.7)	5436(35.6)	
Positive	1119(9.4)	231(16.5)	169(19.0)	1597(10.4)	
Borderline/Unknown	6406(54.1)	584(41.6)	431(48.4)	8258(54.0)	
Molecular subtype					<0.001
Her2-/HR+	3585(30.3)	382(27.2)	169(19.0)	4308(28.2)	
Her2+/HR+	713(6.0)	128(9.1)	95(10.7)	980(6.4)	
Her2+/HR-	406(3.4)	102(7.3)	73(8.2)	615(4.0)	
TNBC	729(6.2)	207(14.7)	122(13.7)	1122(7.3)	
Unknown	6411(54.1)	585(41.7)	432(48.5)	8266(54.1)	
Mean number of involved ALN	15.2±6.5	7.2±7.4	7.0±8.0	14.1±7.2	<0.001
The number of involved ALN					<0.001
0	47(0.4)	149(10.6)	103(11.6)	341(2.2)	
1–3	99(0.8)	304(21.7)	202(22.7)	671(4.4)	
4–9	149(1.3)	394(28.1)	143(16.0)	740(4.8)	
≥10	11,421(96.4)	364(25.9)	189(21.2)	12,872(84.2)	
Unknown	128(1.1)	193(13.7)	254(28.5)	667(4.4)	
Surgery					<0.001
Partial mastectomy	2342(19.8)	301(21.4)	177(19.9)	3030(19.8)	
Mastectomy	9404(79.4)	1017(72.4)	561(63.0)	11,872(77.6) 389(2.5)	
Unknown	98(0.8)	86(6.1)	153(17.2)		
Radiation					0.022
Yes	7300(61.6)	925(65.9)	554(62.2)	9483(62.0)	
No/Unknown	4544(38.4)	479(34.1)	337(37.8)	5808(38.0)	
Chemotherapy					<0.001
Yes	9503(80.2)	1247(88.8)	809(90.8)	12,500(81.7)	
No/Unknown	2341(19.8)	157(11.2)	82(9.2)	2791(18.3)	

Abbreviations: Tis, ductal carcinoma in situ; Tx, primary tumor cannot be assessed; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; TNBC, triple negative breast cancer; ALN, axillary lymph node.

stage, although its prognostic significance was not the same. The nodal status of pN3 in the study is ypN3, which is affected by neoadjuvant chemotherapy. According to our results, the traditional N stage or ypN stage may not able to adequately indicate the prognosis of stage IIIC breast cancer patients.

N3 breast cancer is classified as LABC, which is known for its poor prognosis and regarded as a prelude of distant metastasis.[25] Many studies have reported the prognosis of breast cancer patients with pN3a because ALN metastatic status was more readily available in patients undergoing surgical treatment compared with IMLN and SCLN status. Zeichner et al[10] reported a long-term survival of 161 LABC patients with ≥10 involved lymph nodes, in which the 5-year OS and DFS rates were 66.6% and 59.3%, respectively. However, this study did not consider IMLN or SCLN. Several studies have also reported that the 5-year OS and DFS in patients with pN3a ranged from 58% to 81% and 43% to 66%, respectively. The 5-year OS of pN3a and cN3a in our study was 63.9% and 61.9%, respectively, which was comparable to those of previous studies. The 5-year DFS of pN3a in our study was 40.3%, which was slightly worse than that of previous studies because the majority of patients with pN3a in our study were patients with ICLN metastasis.

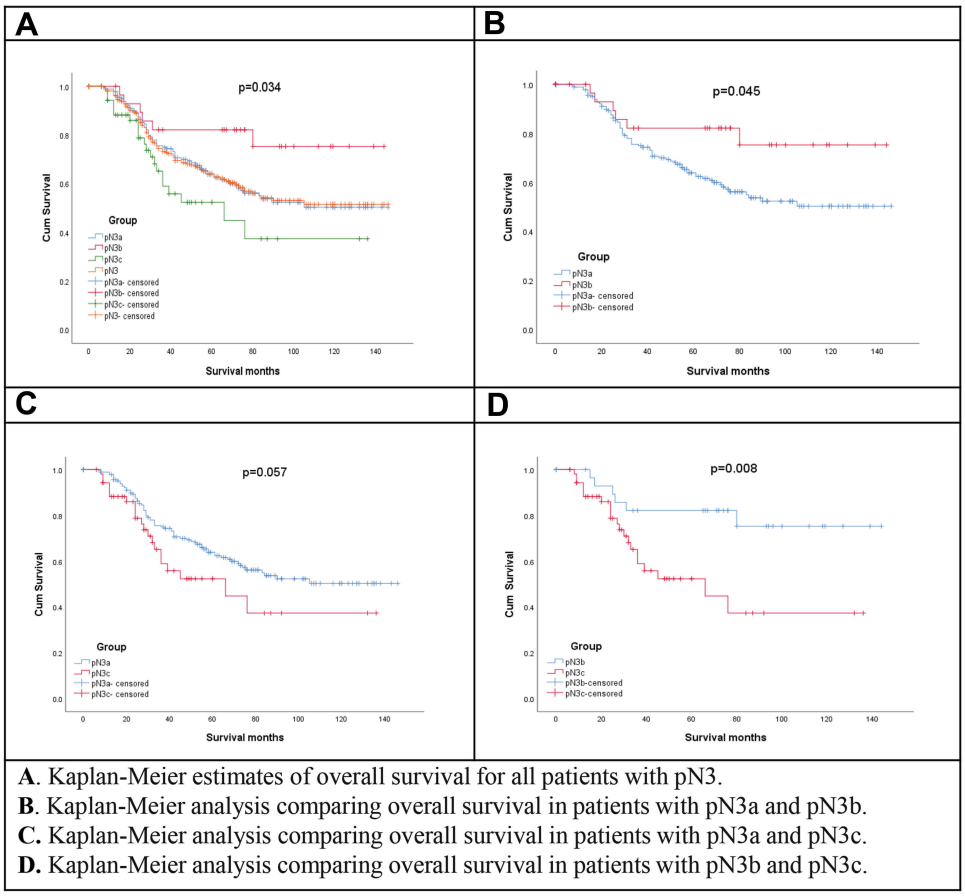
According to the AJCC 6th edition, the presence of IMLN metastases in patients with stage I or II diseases resulted in upstaging to stage III in 2002. In 2012, the AJCC 7th edition further specified N2b: metastases in

Table 3 Clinicopathological Characteristics of M1 Patients

Characteristics	M1(%)
Number of patients	**23,623**
Race	
White	17,784(75.3)
Black	4007(17.0)
Other/Unknown	1832(7.7)
Mean age(years)	60.7±14.2
Age(years)	
≤35	900(3.8)
>35	22,723(96.2)
Tumor location	
Left	11,927(50.5)
Right	11,268(47.7)
Unknown	428(1.8)
Tumor quadrant	
Central	1570(6.6)
Upper-inner	1421(6.0)
Lower-inner	822(3.5)
Upper-outer	5854(24.8)
Lower-outer	1233(5.2)
Overlapping	4769(20.2)
Unknown	7954(33.7)
Primary tumor size	
T0/Tis	162(0.7)
T1	2579(10.9)
T2	6542(27.7)
T3	3393(14.4)
T4	7816(33.1)
TX	3131(13.3)
Histological type	
Ductal	18,000(76.2)
Lobular	2865(12.1)
Mixed	1747(7.4)
Other	1011(4.3)
Grade	
I	1507(6.4)
II	8323(35.2)
III	9966(42.2)
IV	265(1.1)
Unknown	3562(15.1)
ER	
Negative	5664(24.0)
Positive	16,636(70.4)
Borderline/Unknown	1323(5.6)
PR	
Negative	8877(37.6)
Positive	13,225(56.0)
Borderline/Unknown	1521(6.4)
HER-2	
Negative	8795(37.2)
Positive	3217(13.6)
Borderline/Unknown	11,611(49.2)
Molecular subtype	
Her2-/HR+	7223(30.6)
Her2+/HR+	2105(8.9)
Her2+/HR-	1102(4.7)
TNBC	1528(6.5)
Unknown	11,665(49.4)
Mean number of involved ALN	5.5±6.8
The number of involved ALN	
0	1266(5.4)
1–3	2761(11.7)
4–9	1701(7.2)
≥10	1520(6.4)
Unknown	16,375(69.3)
Surgery	
Partial mastectomy	2859(12.1)
Mastectomy	5789(24.5)
Unknown	14,975(63.4)
Radiation	
Yes	7887(33.4)
No/Unknown	15,736(66.6)
Chemotherapy	
Yes	13,046(55.2)
No/Unknown	10,577(44.8)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; TNBC, triple negative breast cancer; ALN, axillary lymph node.

only clinically detected IMLN and in the absence of clinically evident level I, II ALN metastases; and N3b: metastasis in IMLN and ALN. Previous studies showed that patients with IMLN metastasis had worse outcomes, in which the 5-year OS was reported to range from 23.9% to 61.1%,[25–27] where the patient underwent only lymph node surgical resection without current standard management. However, breast cancer patients with N3b treated with the current standard management were recently reported to have a relatively better prognosis than that reported in previous studies, which were a few decades ago, and the 5-year DFS and OS were 56–65% and 76–79%, respectively. Similarly, the present study showed the same prognosis results for N3b: the 5-year



A. Kaplan-Meier estimates of overall survival for all patients with pN3.
B. Kaplan-Meier analysis comparing overall survival in patients with pN3a and pN3b.
C. Kaplan-Meier analysis comparing overall survival in patients with pN3a and pN3c.
D. Kaplan-Meier analysis comparing overall survival in patients with pN3b and pN3c.

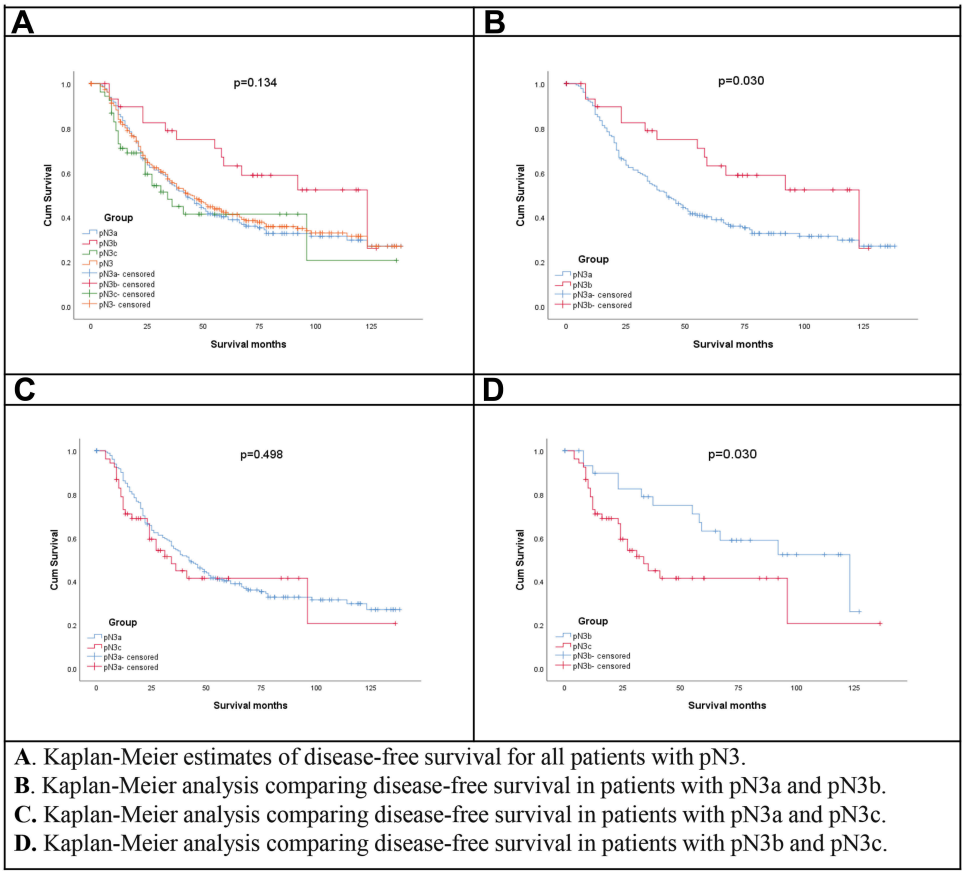
Figure 2 Kaplan–Meier analysis for OS of pN3. (**A**) Kaplan–Meier estimates of overall survival for all patients with pN3. (**B**) Kaplan–Meier analysis comparing overall survival in patients with pN3a and pN3b. (**C**) Kaplan–Meier analysis comparing overall survival in patients with pN3a and pN3c. (**D**) Kaplan–Meier analysis comparing overall survival in patients with pN3b and pN3c.

DFS of pN3b was 63.1%, while the 5-year BCSS of cN3b was 73.4%, and the 5-year OS of pN3b and cN3b were 75.3% and 68.9%, respectively.

In 2001, Brito et al[19] reported that patients with ISLM had better outcomes than patients with stage IV disease. In 2002, the AJCC 6th edition revised the TNM stage of breast cancer and divided ISLM into the N3c stage. Nevertheless, breast cancer patients who present with ISLM still had a poor prognosis. Several studies have reported that the 5-year OS and DFS of N3c range from 33 to 78% and 25 to 51%, respectively. In the present study, the 5-year OS and DFS were 52.4% and 41.5% for pN3c and 53.8% and 49.9% for cN3c, respectively, which were similar to those in previous studies.

Although many studies have reported prognostic outcomes for each subgroup of N3 breast cancer, due to the sample size and the difficulty in obtaining N3b and N3c clinicopathological proof, there have been few studies that systemically compared subgroups in a large consecutive sample of N3 breast cancer. In 2010, Park et al[17] assessed the outcomes of 55 patients with cN3 and reported that the 5-year DFS rates for patients with cN3a, cN3b, and cN3c disease were 62%, 67%, and 51%, and the 5-year OS rates for patients with cN3a, cN3b, and cN3c disease were 80%, 80%, and 78%, respectively. Thereafter in 2015, Yu et al[28] reported the clinical outcomes of 89 patients with pN3 who received current standard management, in which the 5-year DFS rates were 60.3%, 77.8% and 46.3% for patients with ICLN, IMLN, and SCLN, respectively. Although there was no statistically significant difference in prognosis between subgroups regarding their results, a trend was observed that patients with N3b had a better prognosis than those with N3a.

In the present study, we retrospectively screened data on patients presenting with breast cancer at our center, and 284 pN3 patients were finally enrolled. Interestingly, we found that patients with pN3b had a relatively good prognosis. Thereafter, we obtained data on breast cancer



A. Kaplan-Meier estimates of disease-free survival for all patients with pN3.
B. Kaplan-Meier analysis comparing disease-free survival in patients with pN3a and pN3b.
C. Kaplan-Meier analysis comparing disease-free survival in patients with pN3a and pN3c.
D. Kaplan-Meier analysis comparing disease-free survival in patients with pN3b and pN3c.

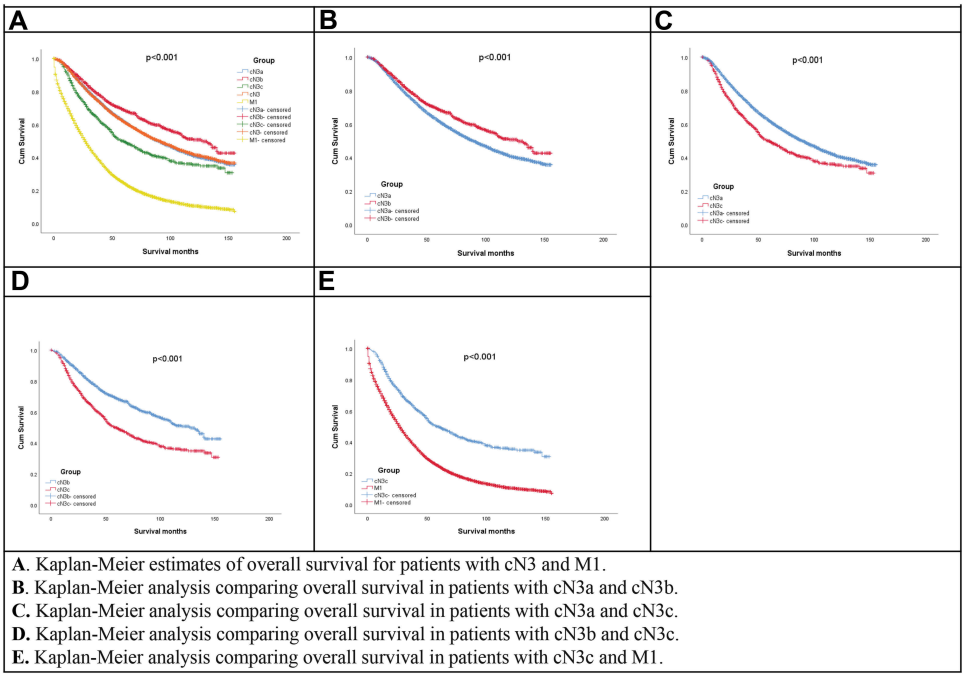
Figure 3 Kaplan–Meier analysis for DFS of pN3. (**A**) Kaplan–Meier estimates of disease-free survival for all patients with pN3. (**B**) Kaplan–Meier analysis comparing disease-free survival in patients with pN3a and pN3b. (**C**) Kaplan–Meier analysis comparing disease-free survival in patients with pN3a and pN3c. (**D**) Kaplan–Meier analysis comparing disease-free survival in patients with pN3b and pN3c.

patients with N3 disease from the SEER database and found that cN3b had a better prognosis than patients in other groups, which was consistent with the results of our center and the two comparison studies mentioned above. According to the AJCC staging system, the prognosis worsened according to the rank order of N3a, N3b, and N3c, which was not consistent with our results. This discrepancy is most likely from the perspective of clinicopathological features. Patients with IMLN metastasis were reported to have favorable outcomes as a result of lower positive ALN involvement,[28] which was consistent with the results of the present study. Besides, IMLN drains approximately 25% of all lymphatics of the breast,[29,30] which is the first station of lymph node metastasis in breast cancer, similar to ALN. Therefore, anatomically, IMLN metastasis in breast cancer may not be a prelude of distant metastasis compared with ICLN and SCLN metastasis. Moreover, based on current standard management, breast cancer patients with IMLN metastasis can be diagnosed accurately, and thus, N3b patients have a relatively favorable prognosis compared with other N3 patients. Further research is needed to elucidate this clinical phenomenon. However, these results were based on the accurate diagnosis of lymph node metastasis, thus accurate diagnosis through IMLN biopsy may still have clinical significance.

Nevertheless, our study has some limitations in terms of its retrospective nature, where potential bias might exist. In addition, in the SEER dataset, data on adjuvant therapy are limited to information on radiation therapy and chemotherapy, while information on endocrine therapy and targeted therapy is unavailable.

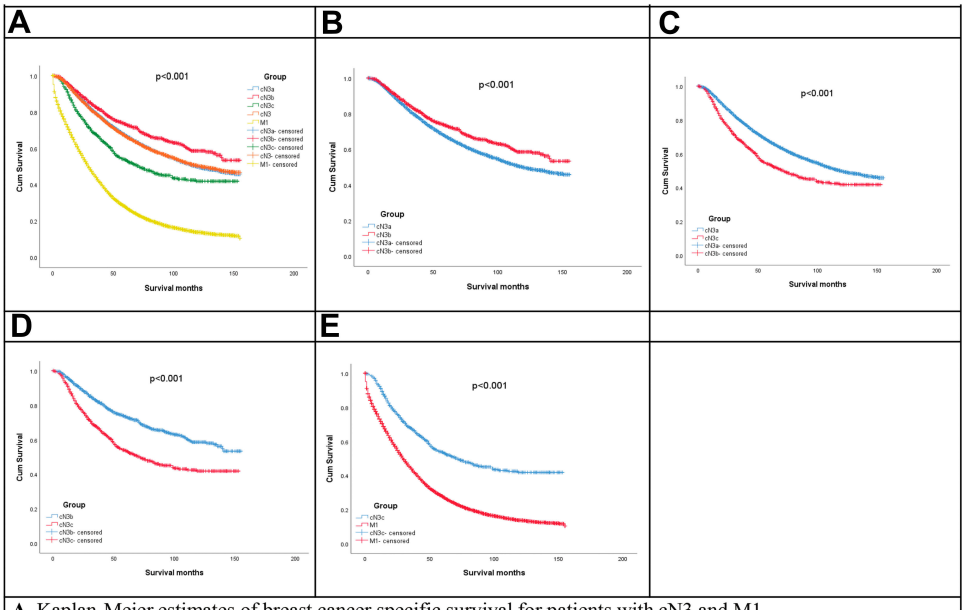
Conclusions

In conclusion, breast cancer patients with N3 disease have a relatively poor prognosis, and patients with N3c had the worst clinical outcomes in the N3 group but much better than patients with M1 disease. N3b patients have a better prognosis than N3a patients in both clinical and pathological stages, and perhaps AJCC should reconsider the



A. Kaplan-Meier estimates of overall survival for patients with cN3 and M1.
B. Kaplan-Meier analysis comparing overall survival in patients with cN3a and cN3b.
C. Kaplan-Meier analysis comparing overall survival in patients with cN3a and cN3c.
D. Kaplan-Meier analysis comparing overall survival in patients with cN3b and cN3c.
E. Kaplan-Meier analysis comparing overall survival in patients with cN3c and M1.

Figure 4 Kaplan–Meier analysis for OS of cN3 and M1. (**A**) Kaplan–Meier estimates of overall survival for patients with cN3 and M1. (**B**) Kaplan–Meier analysis comparing overall survival in patients with cN3a and cN3b. (**C**) Kaplan–Meier analysis comparing overall survival in patients with cN3a and cN3c. (**D**) Kaplan–Meier analysis comparing overall survival in patients with cN3b and cN3c. (**E**) Kaplan–Meier analysis comparing overall survival in patients with cN3c and M1.



A. Kaplan-Meier estimates of breast cancer specific survival for patients with cN3 and M1.
B. Kaplan-Meier analysis comparing breast cancer specific survival in patients with cN3a and cN3b.
C. Kaplan-Meier analysis comparing breast cancer specific survival in patients with cN3a and cN3c.
D. Kaplan-Meier analysis comparing breast cancer specific survival in patients with cN3b and cN3c.
E. Kaplan-Meier analysis comparing breast cancer specific survival in patients with cN3c and M1.

Figure 5 Kaplan–Meier analysis for BCSS of cN3 and M1. (**A**) Kaplan–Meier estimates of breast cancer specific survival for patients with cN3 and M1. (**B**) Kaplan–Meier analysis comparing breast cancer specific survival in patients with cN3a and cN3b. (**C**) Kaplan–Meier analysis comparing breast cancer specific survival in patients with cN3a and cN3c. (**D**) Kaplan–Meier analysis comparing breast cancer specific survival in patients with cN3b and cN3c. (**E**) Kaplan–Meier analysis comparing breast cancer specific survival in patients with cN3c and M1.

traditional N stage and ypN stage basis for stage IIIC breast cancer patients.

Ethical Approval

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University, PLA (The ethics approval number: KY201949).

Informed Consent

A broad informed consent was obtained from all individual participants included in the study. But due to the retrospective nature of the study, specified informed consent was waived. The data was anonymized and maintained with confidentiality.

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Disclosure

The authors declare that they have no conflict of interest.

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