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ORIGINAL ARTICLE

Primary neuroendocrine carcinoma of the breast

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Summary

Purpose: *Primary neuroendocrine carcinoma of the breast (NECB) is a rare distinct type of breast carcinoma. There are only some case reports on this topic published in the past. There is still little known on the optimal treatment outcomes, while a wide variety of treatments is proposed by several authors. In this study we searched the literature on NECB in PubMed to clarify its prognosis and possible optimal therapeutic strategies.*

Methods: *Eighty-six cases of primary NEC, included our case, were collected from PubMed between 1980 and 2013. Initial stage, estrogen receptor (ER)/progesterone receptor (PR)/ human epidermal growth factor receptor 2 (HER-2), surgical procedures, adjuvant treatment and overall survive (OS) were analyzed using the Statistical Package for the Social Sciences (SPSS, v 16.0).*

Results: *All 86 patients enrolled were eligible. Their mean age at diagnosis was 53.9 years (range 25-83) and 1 case was in a male. Overall survival (OS) at 48 months was 83.5%. Patients with enlarged tumor size (10 patients with tumor size >5.0 cm) or advanced stage (stage III 15 patients, stage IV 2 patients) had poor OS (48-month OS: 51.4 vs 97.1% with tumors >5cm vs ≤2cm, respectively and 0.0%, 68.1%, 72.9% and 95.8% in stage IV, III, II and I, respectively). Patients with positive ER, PR or HER-2 had significantly better OS than did those without (ER, p<0.001; PR, p<0.001; HER-2, p=0.082). Besides, all 60 patients with initial primary surgery and without lymph node dissection (LND) showed better OS than those with initial primary surgery without LND, the difference however being not significant (p=0.133).*

Conclusion: *Definite diagnosis and clinical stage are prerequisites in the initial approach in NECB. When detected early the disease may have a good prognosis with combined modality treatment such as chemotherapy, surgery, and radiation therapy. An appropriate therapeutic strategy for this group is also important. Our analysis showed that for patients with early localized disease only primary surgery is recommended and LND is optional. In patients with positive steroid receptors postoperative hormonotherapy is suggested.*

Key words: *breast, estrogen receptor, hormone therapy, neuroendocrine carcinoma, progesterone receptor*

Introduction

NECB is a rare condition, with only some cases been reported in the past since Wade et al.[1]. reported the first case in 1983. The World Health Organization (WHO) classifies mammary carcinomas with neuroendocrine (NE) features as a special tumor entity representing <1% of invasive breast carcinomas [2]. In 2012, WHO divided carcinomas with NE features into 3 categories: neuroendocrine tumor, well-differentiated; neuroendocrine carcinoma, poorly differentiated/ small cell carcinoma; and invasive breast carcinoma with neuroendocrine differentiation [2]. The 3 categories were distinguished, based on histological parameters (histological grade, mucus production, and apocrine differentiation). In general, it may show aggressive clinical behavior, whereas the other, more frequent, breast carcinoma with NE differentiation (cellular mucinous carcinoma and solid papillary carcinoma) is usually of low

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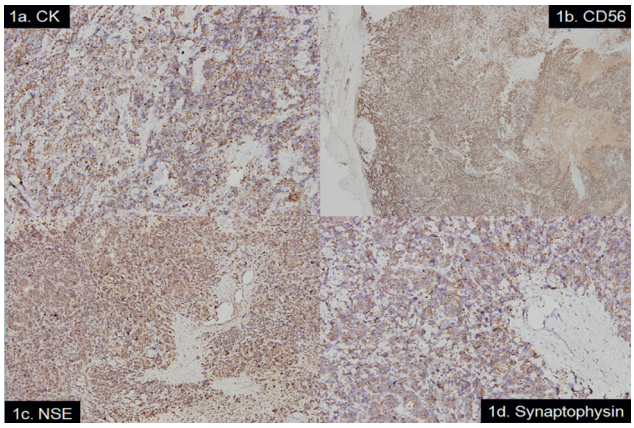

Figure 1. Positive immunohistochemical staining for cytokeratin (**a**), CD56 (**b**), neuron specific enolase (**c**) and synaptophysin (**d**).

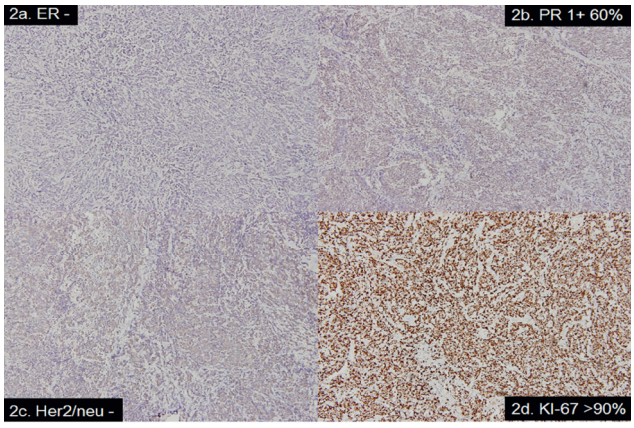

Figure 2. Immunohistochemical staining showing negative ER (**a**), weakly positive PR (**b**), negative HER-2, (**c**) and increased proliferation index (**d**).

grade. For this reason, the treatment and prognosis of this group deserve in-depth discussion. However, there is little known on the optimal treatment and outcomes, and a wide variety of treatments, including surgery, chemotherapy and radiation have been used with different outcomes in the past.

Herein, we reviewed 85 cases who had been published in the past since its first description in 1983 [1,3-41] and reported one case diagnosed at our hospital. In addition, we registered and analyzed all 86 patients at initial stage, ER,PR,HER-2, surgical procedures, adjuvant treatment as well as prognosis.

The aim of this article was the evaluation of prognosis and the clarification of adequate therapeutic strategies for this aggressive tumor.

Methods

We performed a review of the available literature in PubMed using the following key words: "small cell breast cancer", "neuroendocrine breast cancer", and "oat cell carcinoma of the breast". Only articles published between January, 1983 and November, 2013 and with available clinical information were included in the analysis.

Statistics

Survival analysis was estimated by the Kaplan-Meier method using log-rank test. p values<0.05 indicated statistical significance. Multivariate analysis using the Cox proportional hazards model, including all factors with p<0.05 from the univariate analysis, was performed to determine the impact of associated factors. Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc, 16.0, Chicago, Ill).

Results

Case presentation

Our patient was a 53-year-old woman with a 5-month history of a progressively enlarging nodular lesion over the left breast. Ultrasound revealed scattered hypoechoic nodules, < 5 mm in size, in the left breast and enlarged lymph nodes in the left axillary fossa. Diagnostic mammograms also showed scattered isodense nodular densities in the same breast. Excisional biopsy of the largest nodule was done, which revealed relatively small to medium sized, hyperchromatic tumor cells with salt-and-pepper nuclei, inconspicuous nucleoli, focally crushed and molding appearance, large area of necrosis, frequent mitotic figures as well as high proliferative activity. Immunohistochemical stains showed positive cytokeratin (CK), CD56, neuron specific enolase (NSE) and synaptophysin [42-44] (Figure 1), indicating neuroendocrine differentiation. Negative ER, weakly positive PR, HER-2 overexpression, and increased Ki-67 proliferative index (> 90%) were noted (Figure 2). The diagnosis was was poorly differentiated NECB. Clinical stage was cT2N0M0 (stage IIA) according to whole body positron emission tomography (PET) scan. She then underwent modified radical mastectomy (MRM) plus LND (pT2N1M0, stage IIB) on September 17, 2013, followed by adjuvant chemotherapy with cisplatin and etoposide and adjuvant radiotherapy. Two months after the operation, the patient's condition was stable and treatment would continue.

Baseline characteristics

Eighty-five cases were found in PubMed using our criteria since its first description in 1983.

Table 1. Summary of 86 cases with primary NEC of the breast

Year/Author	*Age (years)*	*Sex*	*Size (cm)*	*T*	*N*	*M*	*Stage*	*NSE*	*CgA/B*	*Syn*	*ER*	*PR*	*HER-2*	*F/U (mos)*	*Out-come*
1983 Wade	52	F	10	4	1	1	4	NA	NA	NA	NA	NA	NA	9	D
1992 Papotti	64	F	2	1	0	0	1	-	-	-	-	NA	NA	44	A
1992 Papotti	41	F	3.5	2	1	0	2	+	-	-	-	NA	NA	15	D
1992 Papotti	50	F	3	2	1	0	2	+	+	+	-	-	NA	14	D
1992 Papotti	68	F	5	3	1	0	3	+	+	+	+	+	NA	9	D
1993 Papotti	83	M	1.5	1	0	0	1	+	+	NA	-	NA	NA	84	D
1995 Francois	68	F	4.5	2	0	0	2	+	+	NA	-	-	NA	21	D
1998 Fukunaga	56	F	10	4	1	0	3	+	+	+	-	-	NA	48	A
1998 Sebenik	67	F	3.5	4	0	0	3	+	NA	NA	NA	NA	NA	33	A
2000 Samli	60	F	8	4	1	0	3	+	+	+	+	+	NA	6	AWD
2000 Shin	43	F	1.3	1	0	0	1	+	-	-	-	+	-	30	A
2000 Shin	51	F	1.5	1	0	0	1	+	-	-	+	-	-	25	A
2000 Shin	44	F	2	1	0	0	1	+	-	-	+	-	-	27	A
2000 Shin	64	F	1.8	1	0	0	1	+	-	-	+	-	-	10	A
2000 Shin	46	F	3.4	2	1	0	2	+	-	+	+	+	-	11	AWD
2000 Shin	50	F	2.2	2	1	0	2	+	+	+	+	+	-	35	A
2000 Shin	57	F	2.5	2	1	0	2	+	+	+	+	+	-	10	A
2000 Shin	62	F	5	2	1	0	2	+	+	+	+	+	-	32	AWD
2000 Shin	70	F	4	2	1	0	2	+	+	+	+	+	-	3	A
2000 Yamasaki	41	F	4.5	2	0	0	2	+	+	-	-	NA	NA	16	A
2001 Salmo	46	F	4	2	0	0	2	NA	NA	NA	+	+	NA	9	A
2003 Zekioglu	79	F	1.5	1	0	0	1	+	+	-	+	+	-	24	A
2003 Zekioglu	69	F	1	1	0	0	1	+	+	+	+	+	-	12	A
2003 Zekioglu	72	F	1.5	1	0	0	1	+	-	+	+	+	-	13	A
2003 Zekioglu	60	F	1	1	0	0	1	+	+	+	+	+	+	10	A
2003 Zekioglu	43	F	0.8	1	0	0	1	+	-	+	+	+	-	48	A
2003 Zekioglu	76	F	2.2	2	0	0	2	+	+	+	+	+	-	18	A
2003 Zekioglu	65	F	3.5	2	0	0	2	+	-	+	+	+	NA	16	A
2003 Zekioglu	60	F	2.5	2	0	0	2	+	-	+	+	+	NA	54	A
2003 Zekioglu	68	F	7	3	1	0	3	+	+	+	-	-	1	22	A
2004 Bigotti	56	F	18	4	1	0	3	+	-	+	-	-	-	14	D
2004 Jochems	71	F	3	2	0	0	2	+	-	-	+	+	-	12	A
2004 Mariscal	53	F	5.5	3	1	0	3	NA	NA	+	NA	NA	NA	6	A
2004 Sridhar	58	F	2	1	1	0	2	+	-	-	-	-	NA	18	A
2004 Yamamoto	75	F	2	2	1	0	2	+	-	-	-	-	-	43	A
2004 Yamamoto	53	F	6.5	3	2	0	3	+	-	-	-	-	-	34	A
2005 Adegbola	46	F	1	1	0	0	1	+	+	+	-	-	-	48	A
2005 Adegbola	60	F	1.7	1	0	0	1	+	+	+	-	-	-	20	D
2005 Adegbola	61	F	1.7	1	1	0	2	+	+	-	-	-	-	6	AWD
2005 Stein	54	F	2	1	1	0	2	+	-	-	-	-	NA	24	A
2007 Fujimoto	40	F	2	1	0	0	1	-	+	+	+	+	+	36	A
2007 Kitakata	44	F	4.5	2	1	0	2	+	+	+	-	-	-	22	A
2007 Yaren	76	F	5	2	2	0	3	+	+	-	+	+	-	12	A

Continued on the next page

Year/Author	Age (years)	Sex	Size (cm)	T	N	M	Stage	NSE	CgA/B	Syn	ER	PR	HER-2	F/U (mos)	Out-come
2008 Kim	27	F	3.2	2	2	0	3	+	+	+	NA	NA	NA	18	A
2008 Kinoshita	31	F	6	3	1	0	3	+	+	+	-	-	-	9	D
2008 Sadanaga	33	F	4	2	0	0	2	+	-	-	-	-	-	60	A
2009 Hojo	60	F	3	2	0	0	2	+	-	-	-	-	-	26	D
2009 Quir?s Rivero	41	F	6	3	0	0	3	NA	NA	NA	-	-	-	20	A
2009 Rineer	81	F	NA	NA	NA	NA	3	NA	NA	NA	NA	NA	NA	26	A
2009 Stita	64	F	3	2	0	0	2	NA	+	+	+	+	NA	8	A
2009 Yamaguchi	51	F	2.6	2	1	0	2	+	+	+	-	-	-	12	AWD
2010 Christie	61	F	4.5	2	2	0	3	NA	+	+	-	-	-	3	D
2010 Nicoletta	40	F	3	2	1	0	2	+	+	+	+	+	-	96	A
2011 Honami	54	F	1.3	1	0	0	1	NA	+	+	+	+	-	18	A
2011 Kawanishi	67	F	0.8	1	0	0	1	-	+	+	+	+	-	12	A
2012 Kawasaki	41	F	0	Tis	0	0	0	NA	+	+	+	+	-	10	A
2012 Kawasaki	45	F	0	Tis	0	0	0	NA	+	+	+	+	-	80	A
2012 Kawasaki	41	F	0	Tis	0	0	0	NA	+	+	+	+	+	90	A
2012 Kawasaki	74	F	0	Tis	0	0	0	NA	+	+	+	+	+	91	A
2012 Kawasaki	28	F	0	Tis	0	0	0	NA	+	+	+	+	-	77	A
2012 Kawasaki	30	F	0	Tis	0	0	0	NA	+	+	+	+	-	86	A
2012 Kawasaki	58	F	0	Tis	0	0	0	NA	+	+	+	+	+	96	A
2012 Kawasaki	36	F	0	Tis	0	0	0	NA	+	+	+	+	-	64	A
2012 Kawasaki	38	F	0	Tis	0	0	0	NA	+	+	+	+	-	69	A
2012 Kawasaki	60	F	0.1	1	0	0	1	NA	+	+	+	+	+	84	A
2012 Kawasaki	42	F	0.1	1	0	0	1	NA	+	+	+	+	-	73	A
2012 Kawasaki	43	F	0.1	1	0	0	1	NA	+	+	+	+	-	80	A
2012 Kawasaki	35	F	0.1	1	0	0	1	NA	+	+	+	+	+	10	A
2012 Kawasaki	70	F	0.1	1	0	0	1	NA	+	+	+	+	-	93	A
2012 Kawasaki	72	F	0.1	1	0	0	1	NA	+	+	+	+	+	66	A
2012 Kawasaki	62	F	0.1	1	0	0	1	NA	+	+	+	+	+	88	A
2012 Kawasaki	38	F	0.2	1	0	0	1	NA	+	+	+	+	+	85	A
2012 Kawasaki	73	F	0.3	1	0	0	1	NA	+	+	+	+	+	71	A
2012 Kawasaki	43	F	0.4	1	mic	0	1	NA	+	+	+	+	+	86	A
2012 Kawasaki	42	F	0.5	1	0	0	1	NA	+	+	+	+	+	96	A
2012 Kawasaki	39	F	0.5	1	0	0	1	NA	+	+	+	+	+	74	A
2012 Kawasaki	33	F	0.7	1	0	0	1	NA	+	+	+	+	-	92	A
2012 Kawasaki	36	F	1.5	1	0	0	1	NA	+	+	+	+	+	99	A
2012 Kawasaki	68	F	2.5	2	0	0	2	NA	+	+	+	+	-	68	A
2012 Ochoa	25	F	12	4	3	1	4	NA	NA	+	-	-	-	6	D
2012 Okosh	63	F	1.7	1	0	0	1	+	-	+	-	-	+	44	A
2012 Su	75	F	4	2	0	0	2	-	+	+	+	+	-	20	A
2013 Angarita	51	F	2	4	0	0	3	NA	+	+	+	-	-	13	AWD
2013 Kawasaki	58	F	4.5	2	0	0	2	NA	+	+	-	-	+	49	A
2013 Murthy	34	F	3	2	0	0	2	+	+	+	+	+	-	6	A
2013 Our case	53	F	2.9	2	1	0	2	+	+	+	-	+	-	3	A

+: present, -:absent, A: alive, AWD: alive with disease, D: dead, F: female, M: male, NA: not available information, NSE:neuron specific enolase, Cg A/B: chromogranin A/B, Syn:synaptophysin, ER: estrogen receptor, PR: progesterone receptor, F/U: follow-up, mos: months

Table 2. Stage, treatment modalities, and survival information

Stage	*Surgery*	*LND*	*Adjuvant treatment*	*Patients, N*	*Alive*	*Follow-up (mos, mean)*
0	BCS	-	-	7	7/7	73.9
	Mast	-	-	2	2/2	73.0
I	BCS	-	-	8	8/8	78.5
			R	1	1/1	30.0
			C/R	2	1/2	34.0
			R/H	1	1/1	18.0
			NA	3	3/3	23.7
		+	R	1	1/1	25.0
			H	1	1/1	12.0
			C/R	2	2/2	35.5
	Mast	-	-	6	6/6	78.2
			NA	1	0/1	84.0
		+	-	1	1/1	44.0
			C	1	1/1	10.0
			H	1	1/1	36.0
			NA	2	2/2	18.0
II	BCS	-	C/R	2	2/2 (AWD x 1)	7.5
			NA	1	1/1	18.0
		+	C/R	2	2/2	10.5
			C/H	1	1/1	35.0
	Mast	-	-	1	1/1	68.0
		+	-	1	0/1	26.0
			C	9	8/9 (AWD x 2)	26.4
			R	3	1/3	20.0
			H	2	2/2	16.0
			C/R	3	3/3	35.3
			C/H	2	2/2(AWD x 1)	19.0
			NA	2	2/2	35.0
III	No surgery	-	C/R	1	1/1	26.0
	BCS	-	R	1	1/1	33.0
		+	C	1	0/1	3.0
			R	1	1/1	20.0
			C/R	1	1/1	18.0
	Mast	-	C/H	1	0/1	14.0
		+	-	1	1/1	48.0
			C	2	1/2	7.5
			H	2	1/2	10.5
			C/R	2* (Neo-adjuvant C x 1)	2/2 (AWD x 1)	20.0
			C/H	1	1/1 (AWD x 1)	13.0
			NA	1	1/1	22.0
IV	No surgery	-	C	1	0/1	6.0
	Mast	+	C	1	0/1	9.0

AWD: alive with disease, BCS: breast conserving surgery, C: chemotherapy alone, R: radiation alone, C/R: chemoradiation, C/H: chemotherapy + hormone therapy, R/H: radiation+ hormone therapy, H: hormone therapy, LND: lymph node dissection, Mast: mastectomy, NA: not available information, -: not done, +: done. *neoadjuvant chemotherapy was administered in one case

Table 3. Some clinical factors in relation to OS in 86 patients with primary NECB

Factors	*Patients, N (%)*	*Univariate p-value*	*Multivariate p-value*
Age (years)		0.757	-
<30	3 (3.5)		
30-59	47 (54.7)		
≤60	36 (41.9)		
Tumor size (cm)		<0.001	NS
≤2	45 (52.3)		
2-5	30 (34.9)		
>5	10 (11.6)		
NA	1 (1.2)		
Clinical stage		<0.001	NS
0 (Tis)	9 (10.5)		
1	31 (36.0)		
2	29 (33.7)		
3	15 (17.4)		
4	2 (2.3)		
ER		<0.001	NS
-	29 (33.7)		
+	52 (60.5)		
NA	5 (5.8)		
PR		<0.001	NS
-	26 (30.2)		
+	51 (59.3)		
NA	9 (10.5)		
HER-2		0.082	NS
-	48 (55.8)		
+	18 (20.9)		
NA	20 (23.3)		

-: absent, +: present, NA: not available information, NS: no statistical significance, NECB: neuroendocrine carcinoma of the breast

Table 4. Treatment modalities in relation to overall survival in 60 patients with primary NECB initial surgery

Treatment	*Patients, N (%)*	*Univariate p-value*
Surgery		0.989
BCS	30 (50.0)	
Mast	30 (50.0)	
LND		0.135
No	30 (50.0)	
Yes	30 (50.0)	
Chemotherapy		0.386
No	35 (58.3)	
Yes	25 (41.7)	
Radiotherapy		0.228
No	43 (71.7)	
Yes	17 (28.3)	
Hormonotherapy		0.554
No	52 (86.7)	
Yes	8 (13.3)	

For abbreviations see footnote of Table 2

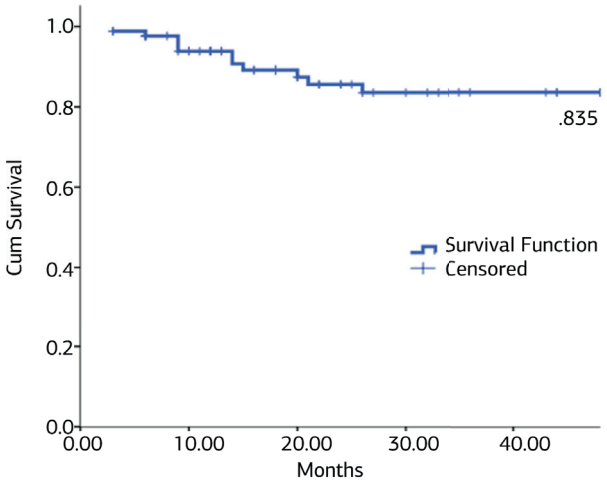

Figure 3. Overall survival of 86 patients.

All 86 patients were enrolled in our analysis. The mean age at diagnosis was 53.9 years (range 25-83), and 1 case was in a male [3] (Table 1).

Staging information was available in all cases. Nine patients (10%) had in situ carcinoma (Tis; stage 0), 31 patients (36%) had localized disease (stage I), 29 patients (34%) had stage II, 15 patients (17%) had locally advanced disease (stage III), and only 2 cases (2%) had metastatic disease on presentation (Table 2).

Tumor size was available in 85 patients. The mean size was 2.75cm, with a range between 0.00 (Tis) and 18.00 cm. T stage was distributed as follows: 45 patients (53%) with size ≤ 2.00 cm, 30 patients (35%) with size 2-5 cm and 10 patients (12%) with size>5.00 cm.

ER were positive in 52 of 81 patients (59%), PR in 51 of 77 patients (66%) and HER-2 overexpression in 18 of 66 patients (27%).

Treatment varied according to stage: all patients with stage 0 (Tis), stage I, stage II, 14 of 15 patients with stage III and only one case with stage IV were initially treated with surgery. Adjuvant treatment with chemotherapy alone, radiotherapy alone, hormonotherapy alone or combined therapy was reported in 87% (13/15) of patients with advanced stage (stage III- IV).

Survival information was available in all cases. With a mean follow-up of 38.1 months (range 3-99), 86% (74/86) of the patients were alive and 79% (68/86) were alive without evidence of recurrent disease. OS rate by stage was 94% in patients with stage I (mean follow-up: 51.7 months), 86% in patients with stage II (mean follow-up: 25.1

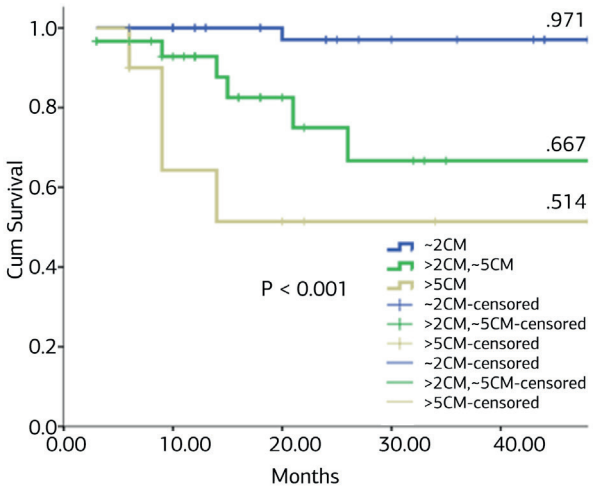

Figure 4. Overall survival of 86 patients in relation to tumor size.

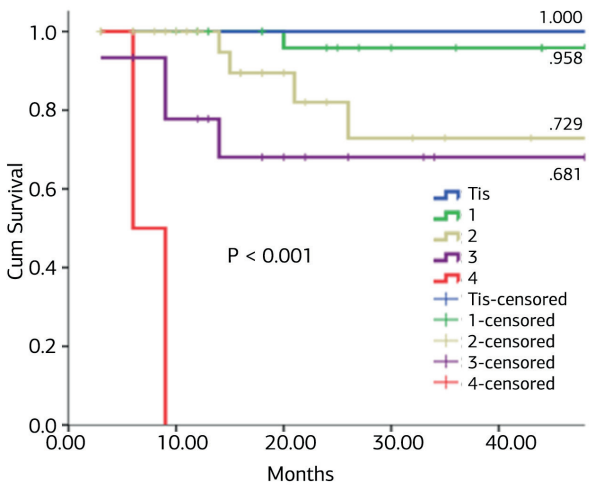

Figure 5. Overall survival of 86 patients in relation to TNM stage.

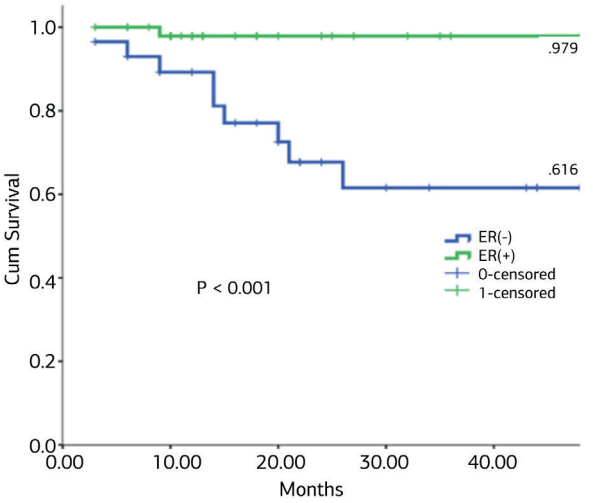

Figure 6. Overall survival of 86 patients in relation to estrogen receptor (ER) status.

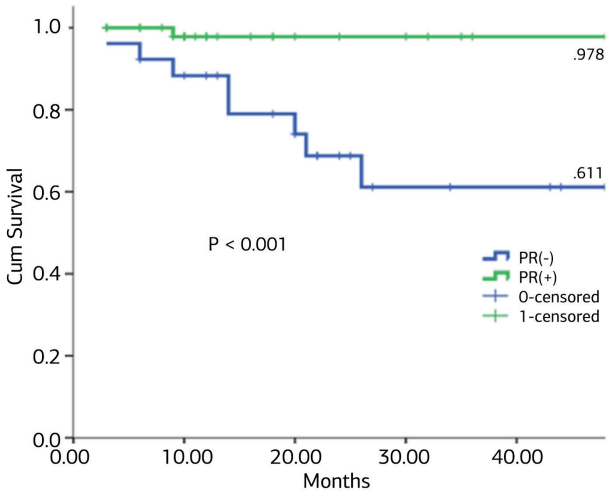

Figure 7. Overall survival of 86 patients in relation to progesterone receptor (PR) status.

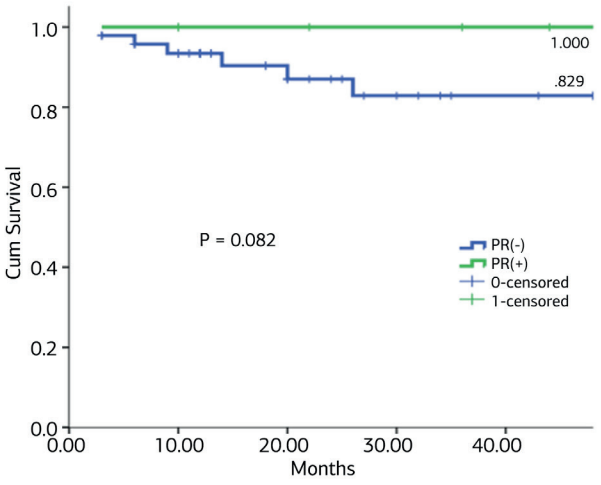

Figure 8. Overall survival of 86 patients in relation to HER-2 status.

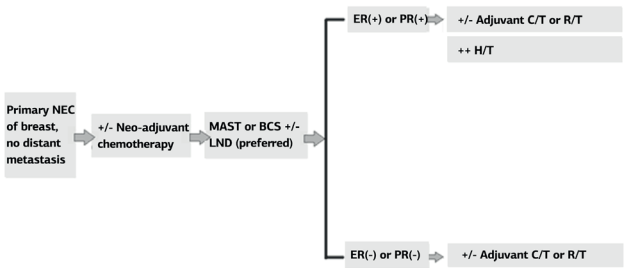

Figure 9. Constructive suggestion of therapeutic strategy in primary NEC of the breast. For abbreviations see text. BCS: breast conserving surgery; C/T: chemotherapy; ER: estrogen receptor; H/T: hormone therapy; LND: lymph node dissection; Mast: mastectomy; PR: progesterone receptor; R/T: radiotherapy.

months), 73% in patients with stage III (mean follow-up: 18.2 months), but 2 patients with stage IV died of NECB.

Statistical analysis of 86 cases

The subgroups by age, tumor size, clinical stage, ER, PR, and HER-2 were evaluated by univariate analysis for associations with OS. OS ratio at 48 months of all 86 patients was 0.835 (Figure 3). Tumor size, clinical stage, and ER, PR showed statistical significance (Table 3). Enlarged tumor size (Figure 4) and advanced cancer stage (Figure 5) showed decreased OS. Besides, patients with ER (Figure 6), PR (Figure 7) or HER-2 (Figure 8) had significantly better OS than those without. Multivariate Cox regression analysis of the above risk factors (those with a p value of <0.05 by univariate analysis) was done, but showed no statistical significance.

Surgical procedures and the choice of adjuvant treatments are shown in Table 4. In all 60 patients with initial primary surgery, we found that patients without lymph node dissection had better OS. Patients who received adjuvant chemotherapy, radiotherapy or didn't receive hormonotherapy had worse OS, but without statistical significance (p=0.386, 0.228 and 0.554, respectively; Tables 2,4).

Discussion

Primary NECB is a rare tumor, which was first recognized in 1963 [45]. However, formal criteria for NECB had not be established until 2003, when WHO Classification of Tumors [46] defined NECB as having >50% neoplastic cells expressing NE markers. Carcinomas with neuroendocrine features were divided into 3 categories, based on histological characteristics. The most important histological factor is the histological grade [47], which is to some extent related to the histologic subtype. For example, solid NEC and atypical carcinoids, described as well-differentiated tumors, have a better prognosis [48] than small cell and large cell NECB, which are poorly differentiated and have an unfavorable prognosis [49]. In our reviewed 86 cases, there was less information about this important classification.

Miremadi et al. had also described that patient outcome is not affected by the size of the NE component [50]. In our univariate analysis, big tumor size was correlated with poor prognosis, but no statistical significance was shown with multivariate analysis. However, the statistical power in our analysis was low due to the small patient number.

Histologically, describing the breast *in situ* component is important because this determines which adjuvant treatment regimens are chosen. Unlike the histogenesis of other common types of NEC where there is evidence of benign NE tumors, these precursor lesions are extremely rare in the breast. Kawasaki et al. had described that NE ductal carcinoma *in situ* (DCIS) could be considered a pre-invasive stage of NECB [51].

Wei et al. stated that most NECB were ER/PR positive and HER-2 negative, and there was marked significant difference with those in other breast cancers [52]. In our reviewed patients, there were similar findings: 52 (60.5%) were ER positive, 51 (59.3%) were PR positive and 48 (55.8%) were HER-2 negative. In univariate analysis, positive receptors seemed to be related to better prognosis, a finding that was cancelled in multivariate analysis. However, the results in this group suggested possible benefits with further hormonotherapy.

Specific recommendations regarding surgical management do not exist. Patients should be treated similarly to ductal carcinoma for which the choice of surgical procedure depends on the tumor's location and clinical stage [53-55]. As the results of our Kaplan-Meier analysis have shown, the patients without LND had better OS. This means that for patients with early localized disease, only primary surgery is recommended and LND is optional. In contrast, advanced-stage patients who underwent mastectomy and LND had poor OS. This revealed that surgical therapy alone may be insufficient. As in the treatment of classic breast adenocarcinoma, regular adjuvant therapy following surgery is suggested and even neo-adjuvant chemotherapy before surgery should be taken into account [7].

In our analysis, the patients given adjuvant chemotherapy seemed to have shorter OS than those without chemotherapy. This also depends on the tumor's status and clinical stage. Advanced-stage patients, almost always received postoperative adjuvant chemotherapy and therefore poor OS may have resulted from their advanced stage of disease. However, the difference was not significant, most likely due to the small patient number and lack of statistical power.

There were various chemoregimens used in those patients with different responses. The real challenge with primary NECB lies in choos-

ing the ideal type of cytotoxic therapy. Currently, there is no information to indicate what the most efficacious regimen is, but the general consensus is to treat this condition with chemotherapy regimens used for common histologic types of breast cancer [56-59] and pulmonary small cell carcinoma [56,60,61].

There are still many unsolved issues in this cancer group. In the past published cases, standard prognostic parameters are not consistently taken into account. In addition, different therapeutic strategies, treatment regimens and their outcomes have not been systemically carried out. Primary NECB, being a rare entity (<1% of breast carcinomas), provided us limited information. So, issues such as histogenesis, optimal adjuvant therapy, and prognosis are still unknown. Prospective additional studies with longer follow-up and higher patient numbers will be needed to address these issues.

Conclusion

NECB is a very aggressive neoplasm for which no standard treatment is defined with certainty due to the small number of cases. According or our metaanalysis, patients with early-stage disease seem to have good prognosis after primary surgery.

Definitive diagnosis and clinical stage are important for initial assessment. Early-stage disease bears good prognosis with combined modality treatment such as chemotherapy, surgery, and radiation therapy. Appropriate therapeutic strategy for this patient group is necessary. Based on our metaanalysis, the results of better OS in patients with positive ER or PR suggest the administration of further adjuvant hormonotherapy (Figure 9). New studies encompassing larger patient populations are needed to analyze and define standard prognostic parameters and to standardize a treatment approach for this very rare neoplasm.

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