Breast Cancer Res Treat (2014) 148:637–644
DOI 10.1007/s10549-014-3207-0

EPIDEMIOLOGY

Impact of histological subtype on long-term outcomes of neuroendocrine carcinoma of the breast

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Received: 8 November 2014 / Accepted: 9 November 2014 / Published online: 16 November 2014

Abstract Although rare, neuroendocrine carcinoma of the breast (NECB) is becoming an increasingly recognized entity. The current literature is limited to case reports and small series and therefore a comprehensive population-based analysis was conducted to investigate the clinicopathologic features and long-term outcomes associated with NECB. We included all patients in the SEER Database from 2003 to 2010 with a diagnosis of NECB. The 2012 WHO classification system was used to categorize patients based on histopathologic diagnosis: well-differentiated neuroendocrine tumors, small/oat cell or poorly differentiated neuroendocrine tumors, adenocarcinoma with neuroendocrine features (ANF), large cell neuroendocrine and carcinoid tumors. Survival analysis was performed for disease specific (DSS) and overall (OS) survival. Of the 284 cases identified, 52.1 % were classified as well-differentiated, 25.7 % small cell, 14.8 % ANF, 4.9 % large cell, and 2.5 % carcinoid. In general, patients presented with advanced disease: 36.2 % had positive lymph node metastases and 20.4 % presented with systemic metastases. Five-year DSS rates for stage I–IV NECB were 88.1, 67.8, 60.5, and 12.4 %, respectively, while five-year OS rates were 77.9, 57.3, 52.9, and 8.9 %, respectively. DSS and OS were significantly different for well-differentiated neuroendocrine tumors and ANFs compared to small cell and carcinoid tumors. On univariate Cox proportional hazards regression, small cell carcinoma was significantly associated with worse DSS (OR 1.97, 95 % CI 1.05–3.67) and OS (OR 2.66, 95 % CI 1.49–4.72) compared to other neuroendocrine tumors. NECB is associated with advanced stage disease at presentation and an unfavorable prognosis for stage II–IV disease and small cell, large cell, and carcinoid histologic subtypes.

Keywords Breast cancer · Neuroendocrine tumors · Carcinoid · Small cell carcinoma · World Health Organization · Lumpectomy · Mastectomy · SEER program

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Introduction

Neuroendocrine carcinoma of the breast (NECB) is a rare form of breast cancer accounting for less than 0.5 % of all cases [1, 2]. While the majority of neuroendocrine tumors arise from neuroendocrine cells in the bronchopulmonary system, gastrointestinal tract, and pancreas, NECB is thought to arise from the divergent differentiation of neoplastic epithelial cells during breast carcinogenesis, rather than preexisting neuroendocrine stem cells. This theory is supported by studies demonstrating that most NECBs have a similar histologic appearance to normal-type breast carcinoma, undifferentiated breast cancer cells are capable of expressing neuroendocrine markers, and the fact that benign neuroendocrine tumors have never been reported in the breast [3–7]. The World Health Organization (WHO) classifies NECB into three subtypes: well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinoma or small cell carcinoma, and invasive breast carcinoma with neuroendocrine differentiation [8].

Implicit in the definition of a neuroendocrine carcinoma of the breast, is the presence of neuroendocrine markers in more than 50 % of cells [9].

Because of its rarity, the current understanding of NECB is limited to case reports and small case series. Previous reports emphasized the aggressive nature and poor prognosis of NECB. However, these studies focused primarily on poorly differentiated NECB [4, 10, 11]. More recently, a systematic review of the literature identified only 108 reported cases of NECB but lacked information on neuroendocrine classification [12]. A population-based analysis of NECB with long-term outcomes is lacking. The purpose of this study, therefore, was to utilize the surveillance, epidemiology, and end results (SEER) database to study a large cohort of NECB, specifically focusing on the histopathological subtypes and prognosis.

Methods

The SEER database was used to identify all patients with a primary NECB. Since the WHO first defined NECB in 2003, only cases from 2003 to 2010 were included. The 2012 WHO classification system was utilized for categorizing and abstracting NECB cases based on the following histopathology: well-differentiated neuroendocrine tumor (SEER code 8246, Fig. 1), poorly differentiated or small/oat cell neuroendocrine tumor (8041–8045), and adenocarcinoma with neuroendocrine features (ANF, 8574). Although not currently listed in the WHO classification system for NECB, also included were carcinoid (8240) and large cell neuroendocrine (8013) tumors.

Descriptive statistics were calculated for demographic (age, gender, race), clinicopathologic (histological subtype, grade, TNM stage, estrogen (ER), and progesterone (PR) receptor status), and treatment (surgery of primary, lymph node surgery, radiation) characteristics. Survival analysis was performed for both disease specific (DSS) and overall (OS) survival using the Kaplan–Meier method. Statistical significance was assessed using the Mantel–Cox log-rank test. Data were unadjusted for demographic, tumor-related, or treatment variables. Figures were created using Graphpad Prism 6.0 (Graphpad Software, Inc; La Jolla, CA).

Univariate and multivariate Cox proportional hazards models were then created to evaluate factors associated with DSS and OS. Independent variables included in the models were age, race, gender, histological subtype, grade, ER/PR status, T, N and M stages, surgery type, receipt of radiation, and whether lymph node sampling was performed. Results are reported as Odds ratio (OR) with 95 %

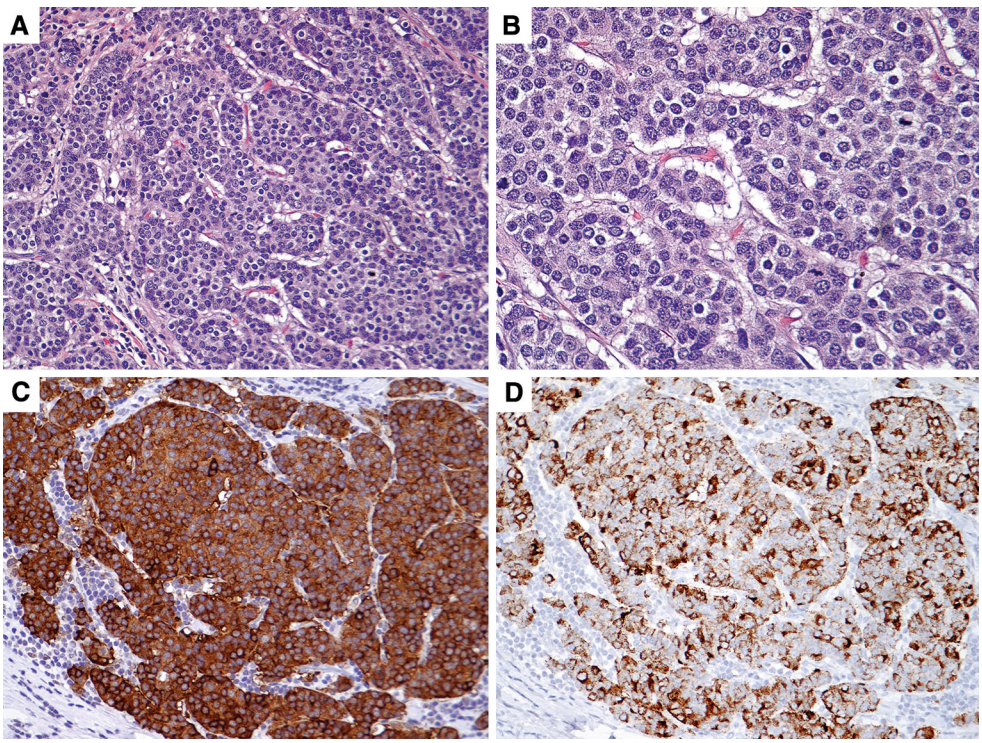

Fig. 1 An example of a well-differentiated neuroendocrine tumor of the breast. **a** H&E stain (×100) demonstrates the solid to trabecular growth pattern often seen with neuroendocrine differentiation. **b** The nuclear features of neuroendocrine differentiation are apparent at higher power (×200) with granular, speckled chromatin. **c** Diffuse staining with synaptophysin. and **d** chromogranin antibodies is present and characteristic (×100)

Table 1 Demographic, clinicopathologic, and treatment characteristics for all patients with neuroendocrine carcinoma of the breast

Characteristic	N (%)
Age	
<50	52 (18.3)
50–59	59 (20.8)
60–69	70 (24.6)
70–79	54 (19.0)
≥80	49 (17.3)
Gender	
Male	9 (3.2)
Female	275 (96.8)
Race	
White	232 (81.7)
Black	40 (14.1)
Other	11 (3.9)
Unknown	1 (0.4)
Histology	
Well-differentiated neuroendocrine	148 (52.1)
Small cell	73 (25.7)
Adenocarcinoma with neuroendocrine features	42 (14.8)
Large cell	14 (4.9)
Carcinoid	7 (2.5)
Grade	
Well-differentiated	28 (9.9)
Moderately-differentiated	56 (19.7)
Poorly differentiated	106 (37.3)
Undifferentiated	21 (7.4)
Unknown	73 (25.7)
Estrogen receptor status	
Positive	132 (46.5)
Negative	98 (34.5)
Unknown	54 (19.0)
Progesterone receptor status	
Positive	101 (35.6)
Negative	123 (43.3)
Unknown	60 (21.1)
T stage	
T1	87 (30.6)
T2	99 (34.9)
T3	24 (8.5)
T4	27 (9.5)
Unknown	47 (16.5)
N stage	
N0	145 (51.1)
N1	67 (23.6)
N2	16 (5.6)
N3	20 (7.0)
Unknown	36 (12.7)
M Stage	
M0	205 (72.2)
M1	58 (20.4)
Unknown	21 (7.4)
Surgery	
Mastectomy	100 (35.2)
Lumpectomy	104 (36.6)
None	79 (27.8)
Unknown	1 (0.4)
Lymph node sampling	
Positive	70 (24.6)
Negative	105 (37.0)
Not examined	97 (34.2)
Unknown	12 (4.2)
Radiation	
None	157 (55.3)
Received	118 (41.5)
Unknown	9 (3.2)
Follow-up	
Alive	171 (60.2)
Died of disease	71 (25.0)
Died of other causes	40 (14.1)
Unknown	2 (0.7)

confidence intervals (CI). Statistics were performed via STATA-MP 11.2 (StataCorp LP; College Station, TX).

Results

Between 2003 and 2010, 284 cases of NECB were recorded in the SEER database: 148 (52.1 %) as well-differentiated neuroendocrine carcinoma, 73 (25.7 %) small cell carcinomas, 42 (14.8 %) with ANF, 14 (4.9 %) large cell neuroendocrine carcinomas, and 7 (2.5 %) carcinoid tumors. Cohort characteristics are listed in Table 1. As expected, most patients were female (96.8 %) and white (81.7 %) while there was a balanced age distribution. A high percentage of tumors (37.3 %) were graded as poorly differentiated though many still expressed ER (46.5 %) and PR (35.6 %) receptors. Many patients had advanced stage disease: 36.2 % presenting with regional lymph node metastases and 20.4 % with systemic metastases. Overall cancer stage was similar across all histologic subtypes, except stage 1 disease predominated in well-differentiated and ANF subtypes (Table 2). Primary surgery was mastectomy in 35.2 % and lumpectomy in 36.6 %, while 27.8 % did not undergo surgery. The latter is congruent

Table 2 Stage stratification for primary neuroendocrine carcinomas based on histological subtype

Stage	Well differentiated	Small cell	Adenocarcinoma with neuroendocrine features	Carcinoid/large cell carcinoma
I	60 (40.5)	23 (31.5)	21 (50.0)	3 (14.3)
II	10 (6.8)	4 (5.4)	2 (4.7)	0
III	38 (25.7)	19 (26.0)	11 (26.2)	6 (28.5)
IV	32 (21.6)	15 (20.5)	5 (11.9)	5 (23.8)
Unknown	8 (5.4)	12 (16.4)	3 (7.1)	7 (33.3)

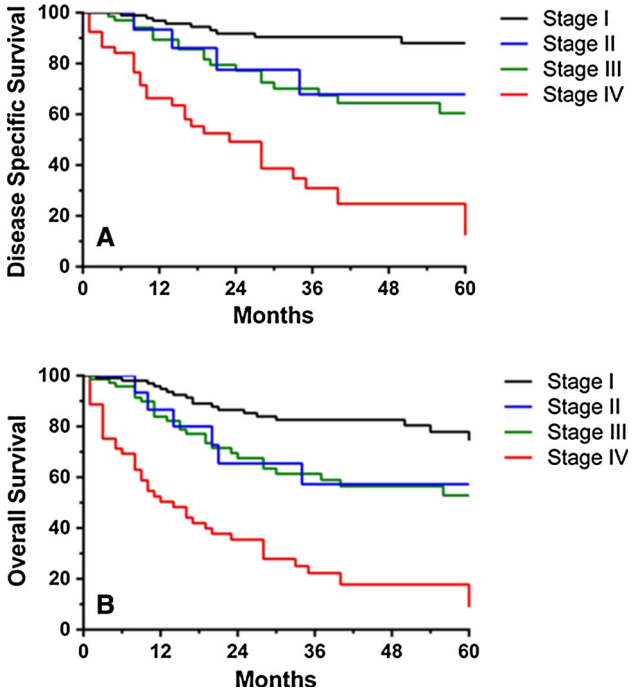

Fig. 2 Stage-stratified disease specific (**a**) and overall (**b**) survival for patients with primary neuroendocrine carcinoma of the breast

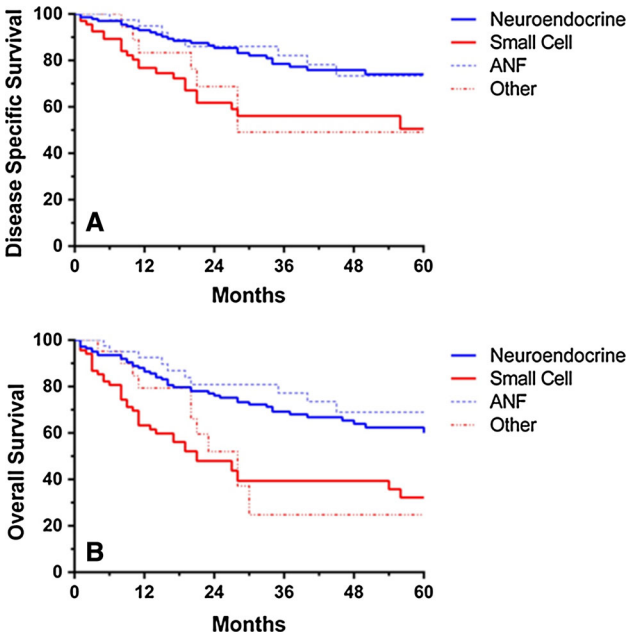

Fig. 3 Disease specific (**a**) and overall (**b**) survival for patients with neuroendocrine carcinoma of the breast stratified by histologic subtype: well-differentiated neuroendocrine carcinoma, small cell neuroendocrine carcinoma, adenocarcinoma with neuroendocrine features (ANF), and other primary neuroendocrine tumors

with the proportion of patients presenting with stage IV or stage unknown disease.

Stage-stratified DSS and OS survival curves are presented in Fig. 2. Five-year DSS rates for stage I–IV NECB were 88.1, 67.8, 60.5, and 12.4 %, respectively ($p < 0.0001$) while 5-year OS rates were 77.9, 57.3, 52.9, and 8.9 %, respectively ($p < 0.0001$). When stratified by histology, long-term outcomes were significantly more favorable for well-differentiated neuroendocrine carcinomas and ANFs compared to small cell carcinomas, large cell carcinomas, and carcinoids (Fig. 3). Five-year DSS rates for well-differentiated neuroendocrine tumors, ANFs, small cell carcinomas, and large cell/carcinoids (combined because of the small numbers) were 74.0, 73.3, 50.5, and 49.1 %, respectively, while 5-year OS rates were 62.4, 68.9, 32.2. and 24.8 %, respectively.

On univariate Cox proportional hazards regression, small cell carcinoma was significantly associated with worse DSS (OR 1.97, 95 % CI 1.05–3.67) and OS (OR 2.66, 95 % CI 1.49–4.72) compared to other neuroendocrine tumors. Black race, poor differentiation, ER/PR receptor negativity, increasing T, N and M stage, and no primary breast surgery were all associated with worse DSS (Table 3). Age $\geq$ 80, poorly differentiated and undifferentiated tumors, ER/PR receptor negativity, advanced T, N and M stages, and no primary breast surgery were all associated with worse OS (Table 3). After controlling for other factors with multivariate Cox hazards regression analysis, the association of small cell carcinoma with DSS (OR 6.46, 95 % CI 0.88–47.68, $p = 0.07$) and OS (1.97, 95 % CI 0.47–8.22, $p = 0.36$) became less statistically significant.

Discussion

Feyrter and Hartmann first made the observation of breast tissue that resembled intestinal carcinoids in 1963 [13]. It

Table 3 Univariate cox proportional hazards analysis for disease specific and overall survival

	Disease specific survival OR (95 % CI), *p* value	Overall survival OR (95 % CI), *p* value
Age		
<50	–	–
50–59	1.56 (0.64–3.83), 0.33	1.69 (0.76–3.74), 0.19
60–69	1.35 (0.56–3.25), 0.51	1.21 (0.55–2.63), 0.64
70–79	1.20 (0.47–3.08), 0.47	1.45 (0.64–3.28), 0.37
≥80	2.04 (0.82–5.07), 0.13	4.25 (1.84–9.79), 0.001
Gender		
Male	–	–
Female	0.37 (0.04–2.98), 0.35	1.22 (0.32–4.64), 0.77
Race		
White	–	–
Black	2.09 (1.03–4.25), 0.04	1.68 (0.86–3.29), 0.13
Other	1.99 (0.56–7.06), 0.29	2.01 (0.60–6.79), 0.26
Histology		
Neuroendocrine	–	–
Small Cell	1.97 (1.05–3.67), 0.03	2.66 (1.49–4.72), 0.001
Adenocarcinoma with neuroendocrine features	0.89 (0.37–2.11), 0.79	0.61 (0.28–1.35), 0.22
Other	1.89 (0.70–5.08), 0.21	2.16 (0.86–5.42), 0.10
Grade		
Well/moderately–differentiated	–	–
Poorly differentiated	2.26 (0.95–5.35), 0.06	3.03 (1.44–6.39), 0.003
Undifferentiated	1.89 (0.54–6.56), 0.33	3.33 (1.15–9.70), 0.03
ER		
Negative	–	–
Positive	0.46 (0.25–0.84), 0.01	0.29 (0.17–0.52), <0.0001
PR		
Negative	–	–
Positive	0.36 (0.19–0.70), 0.003	0.29 (0.16–0.53), <0.0001
T Stage		
T1	–	–
T2	2.14 (0.92–4.99), 0.08	1.48 (0.77–2.86), 0.24
T3	5.13 (1.75–15.07)	3.30 (1.28–8.48), 0.01
T4	14.54 (5.13–41.25), <0.0001	11.55 (4.10–32.55), <0.0001
N Stage		
N0	–	–
N1	2.16 (1.05–4.46), 0.04	1.45 (0.78–2.70), 0.25
N2	3.2 (0.98–10.26), 0.05	3.16 (1.08–9.30), 0.04
N3	47.62 (10.12–224.14), <0.0001	NA
M Stage		
M0	–	–
M1	5.66 (3.02–10.60), <0.0001	8.38 (4.27–16.45), <0.0001
Surgery		
Mastectomy	–	–
Lumpectomy	1.02 (0.50–2.08), 0.96	0.86 (0.47–1.57), 0.63
None	3.44 (1.75–6.78), <0.0001	3.87 (2.07–7.22), <0.0001
Lymph node sampling		
Not Examined	–	–
Examined	0.39 (0.22–0.67), 0.001	0.24 (0.14–0.40), <0.0001

Table 3 continued

	Disease specific survival OR (95 % CI), *p* value	Overall survival OR (95 % CI), *p* value
Radiation		
None	–	–
Received	1.18 (0.67–2.05), 0.57	0.64 (0.39–1.06), 0.09

was not until 1977, that Cubilia and Woodruff reported the first series of primary carcinoid tumors of the breast [14]. Since then, sporadic cases of NECB have been reported throughout the literature. Appreciation of NECB as a separate entity was greatly enhanced when the WHO included NECB in its 2003 classification of tumors report [15]. Despite the increased interest, few large series of NECB have been reported and information on long-term outcomes has been lacking [16].

The diagnosis of NECB can be challenging and depends on careful evaluation of core needle or excisional biopsy specimens. However, routine histological staining is made difficult in that many of the classic histopathological features of neuroendocrine carcinomas occurring in other organs are not present in NECB. Furthermore, mixed growth patterns with invasive ductal or lobular carcinoma, not otherwise specified (NOS) are often present. In one retrospective analysis, the diagnosis of NECB was not recognized initially in over two-thirds of the cases [17]. Histopathologic features concerning for neuroendocrine differentiation (most commonly papillary, nesting, or mixed growth patterns) should be confirmed by immunohistochemical staining with chromogranin, synaptophysin, neuron specific enolase, or other neuroendocrine markers [12, 17]. In addition, NECB should demonstrate an immunoprofile consistent with CK7 positivity and CK20 negativity similar to other breast cancers; nevertheless, there can be variability in this pattern. Interestingly, while many of these tumors demonstrate estrogen and progesterone receptor positivity, their expression is not diagnostic of NECB as ER/PR have been found expressed in other sites and are not universally expressed in breast carcinoma [18].

Because of their rarity as primary breast neoplasms, metastasis from another primary neuroendocrine tumor should be excluded, especially for small cell histology. Markers of pulmonary (TTF-1), GI (CDX-2), or pancreatic origin (PDX-1) should be negative. Careful clinical and radiographic evaluations should exclude other primary sites. Conversely, demonstration of an in situ carcinoma component is helpful for classification as a primary NECB. SEER makes every attempt to include only non-metastatic tumors in the primary site category. However, since this is secondary data, we are unable to conclude with complete certainty that no metastatic neuroendocrine neoplasms originating in other organs or tissues were included as breast primaries.

Within the context of NECB, three distinct subtypes have been described according to the WHO: well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinoma, or small cell carcinoma, and invasive breast carcinoma with neuroendocrine differentiation [8]. Other rare histological subtypes have also been described: carcinoid [19], large cell neuroendocrine [20], endocrine mucoid carcinoma [21], and endocrine ductal carcinoma in situ [22]. Importantly, the impact of histological subtype on long-term outcomes has not been previously investigated. Our study utilized SEER, which advantageously codes these histological subtypes separately, to determine the prognostic value of histology in NECB. We found that small cell carcinomas, large cell carcinomas, and carcinoids behaved similarly and had significantly worse DSS and OS compared to well-differentiated neuroendocrine carcinomas and adenocarcinomas with neuroendocrine features.

Our study confirms previous findings that patients with NECB, in general, present with relatively more advanced disease than primary breast cancers [1]. In our study, 36 % of patients had lymph node metastases and 20 % presented with systemic metastases, significantly greater than patients with invasive ductal carcinoma (IDC, approximately 40 and 10 %, respectively) [23]. Patients with ANF were more likely to present with stage 1 disease, while the other histological subtypes presented at similar stages. Importantly, we found that NECB is associated with worse long-term outcomes compared to IDC [24, 25]. 5-year OS rates of 77.9, 57.3, 52.9, and 8.9 % for stage I–IV disease, respectively, are significantly higher than stage-stratified rates for IDC (100, 93, 72, and 22 %, respectively) [26]. Recently, a stage-matched comparative analysis demonstrated worse survival in NECB compared to IDC-NOS [27].

Our study highlights other demographic and histopathological characteristics with prognostic importance. Age, race, tumor grade, T, N and M staging and receipt of surgery, and lymph node sampling were all associated with survival. Despite its more aggressive behavior, treatment paradigms today are similar to that of IDC. Breast-conserving surgery and mastectomy were used with similar frequency in this population-based study [28–30]. Although the systemic treatment of early NECB typically follows that of IDC [12, 28], immunohistochemistry may be important for guiding adjuvant treatment regimens [31]

as adjuvant endocrine therapies may offer potential in treating susceptible tumors [25]. For example, somatostatin analogs have been used for tumors with confirmed somatostatin-receptor expression [32].

The SEER database is a prospectively collected, population-based cancer registry, which captures 26 % of all cancer cases throughout the United States and provides impressive follow-up. Its large sample size enables the study of less-common diseases such as NECB, on which previous studies had been significantly limited by their small sample size. As with any registry-based analysis, inaccuracies in coding and abstracting may have occurred. In addition, no stringent prospective protocols for pathological review could be applied. Pathologist misinterpretation or misclassification of metastases in the breast from neuroendocrine tumors originating elsewhere is possible. Of note, SEER does not contain information on preoperative comorbidities, postoperative complications, margin status, use of adjuvant systemic therapies, all of which represent important variables in outcome analyses.

These data represent the largest series of NECB cases in the literature. We describe the epidemiological characteristics associated with this rare variant of breast cancer underscoring the advanced stage at presentation and the relatively poor prognosis of NECB. Small cell carcinoma subtype, in particular, is associated with worse DSS and OS compared to well-differentiated NECB and invasive carcinoma with neuroendocrine features. Future studies should consider reporting these subtypes separately based on the differences in prognosis.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Lopez-Bonet E, Alonso-Ruano M, Barraza G, Vazquez-Martin A, Bernado L, Menendez JA (2008) Solid neuroendocrine breast carcinomas: incidence, clinico-pathological features and immunohistochemical profiling. Oncol Rep 20(6):1369–1374
2. Gunhan-Bilgen I, Zekioglu O, Ustun EE, Memis A, Erhan Y (2003) Neuroendocrine differentiated breast carcinoma: imaging features correlated with clinical and histopathological findings. Eur Radiol 13(4):788–793. doi:10.1007/s00330-002-1567-z
3. Hoang MP, Maitra A, Gazdar AF, Albores-Saavedra J (2001) Primary mammary small-cell carcinoma: a molecular analysis of 2 cases. Hum Pathol 32(7):753–757. doi:10.1053/hupa.2001.25603
4. Papotti M, Macri L, Finzi G, Capella C, Eusebi V, Bussolati G (1989) Neuroendocrine differentiation in carcinomas of the breast: a study of 51 cases. Semin Diagn Pathol 6(2):174–188
5. Miremadi A, Pinder SE, Lee AH, Bell JA, Paish EC, Wencyk P, Elston CW, Nicholson RI, Blamey RW, Robertson JF, Ellis IO (2002) Neuroendocrine differentiation and prognosis in breast adenocarcinoma. Histopathology 40(3):215–222
6. Righi L, Sapino A, Marchio C, Papotti M, Bussolati G (2010) Neuroendocrine differentiation in breast cancer: established facts and unresolved problems. Semin Diagn Pathol 27(1):69–76
7. Maluf HM, Koerner FC (1994) Carcinomas of the breast with endocrine differentiation: a review. Virchows Archiv: Int J Pathol 425(5):449–457
8. Lakhani SEI, Schnitt S et al (2012) WHO classification of tumours of the breast, 4th edn. IARC Press, Lyon
9. F A Tavassoli, P Devilee (2003) World Health Organization classification of tumours, pathology and genetics of tumours of the breast and female genital organs In: Press I (ed). Lyon, IARC Press, 32–34
10. Jundt G, Schulz A, Heitz PU, Osborn M (1984) Small cell neuroendocrine (oat cell) carcinoma of the male breast. Immunocytochemical and ultrastructural investigations. Virchows Archiv A, 404 (2):213-221
11. Wade PM Jr, Mills SE, Read M, Cloud W, Lambert MJ 3rd, Smith RE (1983) Small cell neuroendocrine (oat cell) carcinoma of the breast. Cancer 52(1):121–125
12. Adams RW, Dyson P, Barthelmes L (2014) Neuroendocrine breast tumours: breast cancer or neuroendocrine cancer presenting in the breast? Breast 23(2):120–127. doi:10.1016/j.breast.2013.11.005
13. Feyrter F, Hartmann G (1963) On the Carcinoid Growth Form of the Carcinoma Mammae, Especially the Carcinoma Solidum (Gelatinosum) Mammae. Frankfurter Zeitschrift fur Pathologie 73:24–39
14. Cubilia AL, Woodruff JM (1977) Primary carcinoid tumor of the breast. A report of eight patients. Am J Surg Pathol 1(4):283–292
15. Lakhani SR, Ellis I, Schnitt S (2012) WHO classification of tumours of the breast. International agency for research on cancer. IARC Press, Lyon
16. Rovera F, Lavazza M, La Rosa S, Fachinetti A, Chiappa C, Marelli M, Sessa F, Giardina G, Gueli R, Dionigi G, Rausei S, Boni L, Dionigi R (2013) Neuroendocrine breast cancer: retrospective analysis of 96 patients and review of literature. Int J Surg 11(Suppl 1):S79–S83. doi:10.1016/S1743-9191(13)60023-0
17. Tang F, Wei B, Tian Z, Gilcrease MZ, Huo L, Albarracin CT, Resetkova E, Zhang H, Sahin A, Chen J, Bu H, Abraham S, Wu Y (2011) Invasive mammary carcinoma with neuroendocrine differentiation: histological features and diagnostic challenges. Histopathology 59(1):106–115. doi:10.1111/j.1365-2559.2011.03880.x
18. Sica G, Wagner PL, Altorki N, Port J, Lee PC, Vazquez MF, Saqi A (2008) Immunohistochemical expression of estrogen and progesterone receptors in primary pulmonary neuroendocrine tumors. Arch Pathol Lab Med 132(12):1889–1895. doi:10.1043/1543-2165-132.12.1889
19. Upalakalin JN, Collins LC, Tawa N, Parangi S (2006) Carcinoid tumors in the breast. Am J Surg 191(6):799–805. doi:10.1016/j.amjsurg.2005.10.021
20. Tsai WC, Yu JC, Lin CK, Hsieh CT (2005) Primary alveolar-type large cell neuroendocrine carcinoma of the breast. Breast J 11(6):487. doi:10.1111/j.1075-122X.2005.00158.x
21. Capella C, Eusebi V, Mann B, Azzopardi JG (1980) Endocrine differentiation in mucoid carcinoma of the breast. Histopathology 4(6):613–630
22. Tsang WY, Chan JK (1996) Endocrine ductal carcinoma in situ (E-DCIS) of the breast: a form of low-grade DCIS with distinctive clinicopathologic and biologic characteristics. Am J Surg Pathol 20(8):921–943
23. American Cancer Society (2013) Breast Cancer Facts & Figures 2013-2014. American Cancer Society Inc, Atlanta

24. Kwon SY, Bae YK, Gu MJ, Choi JE, Kang SH, Lee SJ, Kim A, Jung HR, Kang SH, Oh HK, Park JY (2014) Neuroendocrine differentiation correlates with hormone receptor expression and decreased survival in patients with invasive breast carcinoma. Histopathology 64(5):647–659. doi:10.1111/his.12306
25. Wei B, Ding T, Xing Y, Wei W, Tian Z, Tang F, Abraham S, Nayeemuddin K, Hunt K, Wu Y (2010) Invasive neuroendocrine carcinoma of the breast: a distinctive subtype of aggressive mammary carcinoma. Cancer 116(19):4463–4473. doi:10.1002/cncr.25352
26. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics, 2014. CA Cancer J Clin 64(1):9–29. doi:10.3322/caac.21208
27. Wang J, Wei B, Albarracin CT, Hu J, Abraham SC, Wu Y (2014) Invasive neuroendocrine carcinoma of the breast: a population-based study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer 14:147. doi:10.1186/1471-2407-14-147
28. Shin SJ, DeLellis RA, Ying L, Rosen PP (2000) Small cell carcinoma of the breast: a clinicopathologic and immunohistochemical study of nine patients. Am J Surg Pathol 24(9):1231–1238
29. Chua RS, Torno RB, Vuletin JC (1997) Fine needle aspiration cytology of small cell neuroendocrine carcinoma of the breast. Acta cytologica 41(4 Suppl):1341–1344
30. Sebenik M, Nair SG, Hamati HF (1998) Primary small cell anaplastic carcinoma of the breast diagnosed by fine needle aspiration cytology: a case report. Acta Cytol 42(5):1199–1203
31. Watrowski R, Jager C, Mattern D, Horst C (2012) Neuroendocrine carcinoma of the breast–diagnostic and clinical implications. Anticancer Res 32(11):5079–5082
32. Saeed A, Rehman A, Zaidi SA, Shaukat T, Jamil K, Abdullah K (2011) Neuroendocrine carcinoma of breast. J Coll Phys Surg Pak: JCPSP 21(6):371–373