HHS Public Access

Author manuscript

Ann Surg Oncol. Author manuscript; available in PMC 2023 October 01.

Primary Breast Neuroendocrine Tumors: An Analysis of the National Cancer Database

Enrique O. Martinez, BS[1], **Julie M. Jorns, MD**[2], **Amanda L. Kong, MD, MS, FSSO, FACS**[1,3], **Julie Kijak, BS**[1], **Wen-Yao Lee**[4,5], **Chiang-Ching Huang, PhD**[5], **Chandler S. Cortina, MD, MS, FSSO, FACS**[1,3]

[1]Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI

[2]Department of Pathology, Medical College of Wisconsin, Milwaukee, WI

[3]MCW Cancer Center, Milwaukee, WI

[4]Chang Gung University, Taoyuan City, Taiwan

[5]Zilber School of Public Health, University of Wisconsin at Milwaukee, Milwaukee, WI

Abstract

Background.—Primary breast neuroendocrine tumors (BNETs) represent < 1% of breast cancers. Diagnosing BNETs can be challenging, and a limited amount of cohort data currently exists in literature. We aimed to describe primary BNET characteristics, treatment modalities, and survival outcomes through the National Cancer Database (NCDB).

Methods.—A retrospective cohort analysis was performed using the NCDB from 2004 to 2017. BNET cases were compared with patients with invasive ductal carcinoma (IDC). A matched IDC cohort was created by matching patient age, race, and disease stage. Kaplan–Meier analysis was performed, and hazard ratios (HR) were calculated through the bootstrap sampling method.

Results.—A total of 1389 BNET and 1,967,401 IDC cases were identified. When compared with IDC patients, BNET patients were older, had more comorbidities, and were more often male ($p < 0.01$). BNETs were larger, higher grade, and more frequently hormone receptor negative ($p < 0.01$). While BNET patients were treated with surgery and radiotherapy ($p < 0.01$) less often compared with IDC patients, they presented at later disease stage ($p < 0.001$) and received systemic treatment more frequently (53.5% vs. 40%, $p < 0.01$). Patients with BNET had increased mortality compared with the matched IDC cohort: stage 1 HR 1.8, stage 2 HR 2.0, stage 3 HR 1.8, and stage 4 HR 1.5 ($p < 0.001$ for all).

Conclusion.—Patients with BNET tend to present at higher clinical stages, are more frequently hormone receptor negative, and have inferior overall survival compared with patients with IDC. Further treatment strategies and studies are needed to elucidate optimal therapies to maximize patient outcomes.

C. S. Cortina, MD, MS, FSSO, FACS, ccortina@mcw.edu.

DISCLOSURES The authors have no disclosures to report.

Neuroendocrine tumors (NETs) account for approximately 2% of solid organ malignancies diagnosed in the USA.[1] NETs commonly have pulmonary or gastrointestinal origin, and there has been a sixfold increase in their incidence from 1973 to 2012.[2] While survival rates for more common NET histologies are poor overall, there has been improvement over time.[2,3] However, for less common histologies, such as primary breast neuroendocrine tumors (BNETs), prognosis data have shown mixed results, likely secondary to the limited number of reported cases and available data.[2,4] While the majority (80%) of breast cancers are of ductal origin,[5,6] BNETs represent < 1% of all breast cancer subtypes and clinically present similarly to other histological breast cancer subtypes.[4,7] Biomarkers such as chromogranin and synaptophysin can assist in distinguishing BNETs from other breast cancer subtypes; however, diagnosing a BNET can be challenging given the immunohistochemical similarities to other breast pathologies such as mucinous and solid papillary carcinoma.[8]

There is a paucity of large cohort data on BNETs given that the majority of the published literature are case studies and small cohorts.[9,10] Current primary treatment is surgical resection, but no clinical trials exist to establish optimal adjuvant therapy options, owing to its rarity.[4,9,10] Utilizing a large national dataset, we aimed to describe the clinical characteristics of BNETs, report overall survival (OS) rates by disease stage, and compare survival with a matched cohort of patients with invasive ductal carcinoma (IDC).

METHODS

A retrospective cohort analysis was performed using the American College of Surgeon's National Cancer Database (NCDB) from the years 2004–2017. As these data are deidentified, this study was deemed exempt by our institution's Institutional Review Board for human subject research. BNET cases were identified by breast International Classification of Disease (ICD) histology codes for small cell carcinoma (8041), carcinoma with neuroendocrine differentiation/features (8574/3), and well-differentiated neuroendocrine carcinoma (8246/3). Cases without invasive disease were excluded. A comparative matched IDC cohort was then created by matching BNET patients to a contemporary cohort of IDC patients by race, age, and disease stage (utilizing the AJCC 7th staging edition). Comparative statistics for the BNET and IDC cohorts were performed through *t*-tests and chi-squared tests. Kaplan–Meier analysis was performed to assess and compare survival of BNETs with the matched IDC cohort for each disease stage. Hazard ratios (HR) were calculated with 95% confidence intervals (CI) through the bootstrap sampling method. All analyses were performed using R version 4.0.5, and a *p*-value of 0.05 was predetermined as significant.

RESULTS

A total of 1389 BNET and 1,967,401 IDC cases were identified from the NCDB. Patients with BNETs were primarily ≥ 50 years of age (82.9%), female (97.9%), and non-Hispanic white (78%) (Table 1). The majority of both IDC and BNET cases were diagnosed in the Southern (34%) and Midwestern (24%) USA, and approximately 85% of cases were from metropolitan areas. BNETs were more frequently diagnosed in academic centers compared

with IDC (33.0% vs. 28.0%, $p < 0.001$) and were more frequently seen in uninsured individuals (2.8% vs. 2.0%, $p < 0.001$).

When compared with IDC patients, patients with BNET had a higher Charlson–Deyo comorbidity index, defined as a score of ≥ 2 (5.4% vs. 3.4%, $p < 0.001$), and they were seen in males more frequently (2.1% vs. 1.0%, $p < 0.01$). BNET patients were diagnosed at more advance stage, had higher tumor grade and larger tumor size, and had a greater percent of nodal involvement compared with those with IDC ($p < 0.001$). BNETs were more likely to be to be ER negative (32% vs. 20%, $p < 0.001$) and PR negative (37% vs. 29%, $p < 0.001$) compared with IDCs. HER2 status was only available for 60.8% of the BNET cohort, and among those with available data, BNETs were more likely to be HER2 negative compared with IDC cases (58.7% vs. 45.6%, $p < 0.001$).

Treatment and management in BNET patients differed from those of IDC patients. Surgical resection was omitted more frequently for BNET patients than IDC patients, being used in 24% of BNET patients compared with only 6.9% of IDC patients ($p < 0.001$). Lumpectomies were performed in only 40.0% of BNET cases versus 55.1% of IDC patients ($p < 0.001$), mastectomies were performed in 34.7% of BNET patients versus 37.6% of IDC patients ($p < 0.001$), and postmastectomy breast reconstruction was more common in patients with IDC (6.3% vs. 11.4%, $p < 0.001$). While patients with BNETs received radiation therapy (45.7% vs. 53.1%, $p < 0.01$) and immunotherapy (1.9% vs. 5.2%, $p < 0.001$) less often, systemic chemotherapy was used more frequently (53.6% vs. 40%, $p < 0.01$) compared with patients with IDC.

Survival data were available for 1141 BNET patients and were compared with an IDC cohort that was matched by patient age, race, and disease stage during the same time interval. Five-year overall survival (OS) rates for BNETs were 80% for stage 1, 63% for stage 2, 45% for stage 3, and 13% for stage 4 (Table 2). Patients with BNETs demonstrated lower OS for all disease stages when compared with the matched IDC cohort (Fig. 1, $p < 0.001$). Compared with IDC patients, mortality risk was higher for BNET patients for all disease stages: stage 1 HR 1.8 (95% CI 1.5–2.3, $p < 0.001$), stage 2 HR 2.0 (95% CI 1.6–2.5, $p < 0.001$), stage 3 HR 1.8 (95% CI 1.3–2.3, $p < 0.001$), and stage 4 HR 1.5 (95% CI 1.3–1.8, $p < 0.001$).

DISCUSSION

BNETs are rare and represent < 1% of breast cancer subtypes. Using the NCDB, we analyzed the largest BNET cohort to date and found that BNETs tend to be higher grade and more frequently hormone receptor negative, and present at more advanced disease stage, than IDC. While tumor biology and treatment methods varied between the BNET cohort and the matched IDC cohort, it appears that patients with BNETs have higher likelihood of mortality, and further data are needed to elucidate optimal oncologic treatment strategies for this rare subtype of breast cancer.

NETs have unique histologic characteristics that distinguish them from nonneuroendocrine cancers. However, there are no specific biomarkers to specifically differentiate BNETs from

other NETs, making diagnosis more challenging. Based on multiple case report analyses, chromogranin and synaptophysin are the most consistent neuroendocrine biomarkers that may support diagnosis of BNET, although these may also be present in NETs from other primary organ sites and can also be seen in other breast cancer subtypes.[10-16] Other biomarkers that can support neuroendocrine differentiation include keratin 5/6, enolase, and thyroid transcription factor-1.[17] However, the data on neuroendocrine biomarkers for BNETs are heterogeneous, and there is no one specific marker for BNETs or other NETs. Thus, diagnosis must be made with careful correlation of clinical context, morphology, and biomarker profile.[18,19] In addition to neuroendocrine markers, the World Health Organization, European Neuroendocrine Tumor Society, and North American Neuroendocrine Tumor Society have established recommendations to use Ki-67 percentage as a NET tumor grading biomarker: grade 1 (≤ 2%), grade 2 (3–20%), or grade 3 (> 20%), which have been found to correlate with disease prognosis.[7,20-22] While we continue to see literature supporting the use of neuroendocrine biomarkers in breast tumors to diagnose BNETs, only recently has there been effort to establish standardized diagnostic criteria for NETs across organ sites and develop best practice guidelines. Additionally, data on the neuroendocrine biomarkers described above are still evolving (Fig. 2).[21] As the field of genetics advances, there is emerging research on epigenetic markers and micro-RNAs that may aid in precisely diagnosing BNETs and differentiating them from other types of NETs in the near future.[23]

Previous case reports and smaller cohort analyses have revealed some findings similar to those presented here. Using the Surveillance, Epidemiology, and End Results (SEER) database, Wang and colleagues assessed 143 BNET cases in 2014 and also found that BNETs were diagnosed at higher stage and with greater tumor size compared with patients with IDC or lobular carcinoma.[10] Angarita et al. reviewed 80 cases of BNETs published in literature and also found that surgical intervention is performed less frequently and may be secondary to advanced disease stage.[12] While the majority of cases in our cohort were hormone receptor negative, previous analyses and reviews have reported BNET cases to be hormone receptor positive.[10-12] Given the size of our cohort compared with previous series, it appears that the majority of BNETs are, in fact, hormone receptor negative.

Our analysis found BNETs to be seen more frequently in uninsured patients when compared with patients with IDC. Lack of health insurance is a known contributor to lower rates of breast cancer screening, which results in higherstage disease at time of diagnosis and also can contribute to delays in cancer treatment.[24,25] The challenges in diagnosing BNETs combined with lower rates of screening and delays in treatment among the uninsured population contribute to higher incidence of BNETs compared with IDC. Additionally, similar to the SEER analysis by Wang and colleagues, our analysis found that BNETs have a higher predilection for male patients compared with IDC.[10] This perhaps may be secondary to the potential protective effects of estrogen seen in females given that estrogen exposure appears to be protective against the development of general neuroendocrine tumors.[26,27]

Significant treatment differences were seen between the BNET and IDC cohorts. Given that 17.9% of BNET patients were diagnosed with stage 4 disease, compared with only 3.7% of IDC patients, it is expected that patients with BNETs received surgery and radiation

therapy less frequently than IDC patients, given that the clinical benefit of local therapy for stage 4 breast cancer is unclear.[28-30] Additionally, because BNET patients were more likely to have hormone receptor negative tumors and stage 4 disease, these factors may explain why BNET patients received systemic chemotherapy more frequently than their matched IDC counterparts. While a slightly smaller percentage of BNET patients underwent mastectomy than those with IDC, postmastectomy radiation therapy was much lower in BNET patients; however, the addition of postmastectomy radiation therapy for patients with hormone receptor negative disease has not been shown to definitively decrease local recurrence or influence survival.[31]

Even when creating an IDC patient cohort matched by race, age, and stage, patients with BNETs had a statistically significantly increased risk of mortality for all disease stages. This finding is possibly secondary to tumor biology as BNET tumors were more frequently hormone receptor negative, HER2 negative (for available cases), and had higher tumor grade. Wang et al. hypothesized that estrogen receptor status in BNETs does not provide a prognostic benefit given the high incidence of hormone receptor positivity treated with systemic agents, yet continued lower survival rates.[10] If so, BNETs may be more resistant to current endocrine therapy options than IDCs, and this is a space for future research. Recent reports have found that, in patients with triple-negative breast cancer, socioeconomic variables can have a profound influence on clinical treatment and outcomes, and while we found no difference in race between the BNET and IDC patients and only a small percentage of patients in both cohorts did not have insurance, there may be other external factors that may have influenced survival and were not captured by this analysis.[32,33]

Limitations to this study include those that are intrinsic to the NCDB such as general coding errors, including those that may misdiagnose patients who should have been classified into the three ICD histology codes that were used for this analysis. Prior to 2009, the NCDB did not obtain data on HER2 status, and thus patients could only be sufficiently analyzed in the setting of their hormone receptor status only, rather than as HER2 positive or triple negative, and this may have masked biological differences between the two cohorts. The NCDB does not provide disease-specific survival data, which is of particular importance when comparing mortality for rare cancer subtypes. Moreover, given the low number of male patients in the BNET group, we were unable to sufficiently assess whether a survival difference exists between males and females with BNETs given that they appear to exist for more common breast cancer subyptes.[34] Nevertheless, this series presents the largest cohort of BNET patients to date and provides valuable insight into this rare entity.

CONCLUSIONS

In this analysis of patients with BNETs in the NCDB, we found that patients with BNETs were diagnosed at later stages, had less favorable tumor characteristics, and had lower OS by stage compared with IDC patients. Pathological diagnosis remains a challenge, and developing diagnostic methods show promise. Clinicians and patients should be aware of lower OS rates with BNETs as this may aid in guiding multidisciplinary oncologic treatment decisions. Future study is needed to elucidate optimal treatment strategies for this rare and aggressive breast cancer subtype.

FUNDING

The funding was provided by National Center for Advancing Translational Sciences (Grant No. UL1TR001436).

REFERENCES

1. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia. 2017;19(12):991–1002. 10.1016/j.neo.2017.09.002. [PubMed: 29091800]
2. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–42. 10.1001/jamaoncol.2017.0589. [PubMed: 28448665]
3. Alese AOB, Jiang R, Shaib W, et al. High-grade gastrointestinal neuroendocrine carcinoma management and outcomes: a National Cancer Database study. Oncologist. 2020;25(5):e877. 10.1634/theoncologist.2020-0135. [PubMed: 32395915]
4. Inno A, Bogina G, Turazza M, et al. Neuroendocrine carcinoma of the breast: current evidence and future perspectives. Oncologist. 2016;21(1):28–32. 10.1634/theoncologist.2015-0309. [PubMed: 26659223]
5. Li CI, Daling JR. Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. Cancer Epidemiol Biomark Prev. 2007;16(12):2773–80. 10.1158/1055-9965.EPI-07-0546.
6. Keeney MG, Couch FJ, Visscher DW, Lindor NM. Non-BRCA familial breast cancer: review of reported pathology and molecular findings. Pathology. 2017;49(4):363–70. 10.1016/j.pathol.2017.03.002. [PubMed: 28450088]
7. Zagami P, Kandaraki E, Renne G, et al. The rare entity of bilateral and unilateral neuroendocrine metastases to the breast: a case series and literature review. Ecancermedicalscience. 2020;14:1123. 10.3332/ecancer.2020.1123. [PubMed: 33209114]
8. Trevisi E, La Salvia A, Daniele L, et al. Neuroendocrine breast carcinoma: a rare but challenging entity. Med Oncol. 2020;37(8):70. 10.1007/s12032-020-01396-4. [PubMed: 32712767]
9. Irelli A, Sirufo MM, Morelli L, D'Ugo C, Ginaldi L, De Martinis M. Neuroendocrine cancer of the breast: a rare entity. J Clin Med. 2020;9(5):1452. 10.3390/jcm9051452.
10. Wang J, Wei B, Albarracin CT, Hu J, Abraham SC, Wu Y. Invasive neuroendocrine carcinoma of the breast: a population-based study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer. 2014;14:147. 10.1186/1471-2407-14-147. [PubMed: 24589259]
11. Özdirik B, Kayser A, Ullrich A, et al. Primary neuroendocrine neoplasms of the breast: case series and literature review. Cancers (Basel). 2020;12(3):733. 10.3390/cancers12030733.
12. Angarita FA, Rodríguez JL, Meek E, Sánchez JO, Tawil M, Torregrosa L. Locally-advanced primary neuroendocrine carcinoma of the breast: case report and review of the literature. World J Surg Oncol. 2013;11:128. 10.1186/1477-7819-11-128. [PubMed: 23734899]
13. Krawczyk N, Röwer R, Anlauf M, et al. Invasive breast carcinoma with neuroendocrine differentiation: a single-center analysis of clinical features and prognosis. Geburtshilfe Frauenheilkd. 2021;82(1):68–84. 10.1055/a-1557-1280. [PubMed: 35027862]
14. Deftos LJ. Chromogranin A: its role in endocrine function and as an endocrine and neuroendocrine tumor marker. Endocr Rev. 1991;12(2):181–7. 10.1210/edrv-12-2-181. [PubMed: 2070778]
15. D'Alessandro M, Mariani P, Lomanto D, Carlei F, Lezoche E, Speranza V. Serum neuron-specific enolase in diagnosis and follow-up of gastrointestinal neuroendocrine tumors. Tumour Biol. 1992;13(5–6):352–7. 10.1159/000217786. [PubMed: 1290031]
16. Makki J Diversity of breast carcinoma: histological subtypes and clinical relevance. Clin Med Insights Pathol. 2015;8:23–31. 10.4137/CPath.S31563. [PubMed: 26740749]
17. Baudin E, Gigliotti A, Ducreux M, et al. Neuron-specific enolase and chromogranin A as markers of neuroendocrine tumours. Br J Cancer. 1998;78(8):1102–7. 10.1038/bjc.1998.635. [PubMed: 9792158]

18. Agoff SN, Lamps LW, Philip AT, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol. 2000;13(3):238–42. 10.1038/modpathol.3880044. [PubMed: 10757334]
19. Tremelling A, Samuel S, Murray M. Primary small cell neuroendocrine carcinoma of the breast: a case report and review of the literature. Int J Surg Case Rep. 2017;38:29–31. 10.1016/j.ijscr.2017.07.002. [PubMed: 28734185]
20. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? Hum Pathol. 2020;96:8–33. 10.1016/j.humpath.2019.12.002. [PubMed: 31857137]
21. Nadler A, Cukier M, Rowsell C, et al. Ki-67 is a reliable pathological grading marker for neuroendocrine tumors. Virchows Arch. 2013;462(5):501–5. 10.1007/s00428-013-1410-8. [PubMed: 23588555]
22. Rakha EA, Reis-Filho JS, Wu Y. Neuroendocrine Tumour, Neuroendocrine Carcinoma. WHO classification of Tumours: Breast Tumours. 5th ed. Lyon France:IARC press, 2019:156–161.
23. Geisler L, Mohr R, Lambrecht J, et al. The role of miRNA in the pathophysiology of neuroendocrine tumors. Int J Mol Sci. 2021;22(16):8569. 10.3390/ijms22168569. [PubMed: 34445276]
24. Highfield L Spatial patterns of breast cancer incidence and uninsured women of mammography screening age. Breast J. 2013;19(3):293–301. 10.1111/tbj.12100. [PubMed: 23521583]
25. Jerome-D'Emilia B, Suplee PD, Robles-Rodriguez E, D'Emilia W. The impact of delays in low-income women's breast cancer experiences. Cancer Nurs. 2021;44(1):E43–52. 10.1097/NCC.0000000000000878. [PubMed: 32804755]
26. Estrella JS, Ma LT, Milton DR, et al. Expression of estrogen-induced genes and estrogen receptor β in pancreatic neuroendocrine tumors: implications for targeted therapy. Pancreas. 2014;43(7):996–1002. 10.1097/MPA.0000000000000203. [PubMed: 25058880]
27. Qiu W, Christakis I, Stewart AA, et al. Is estrogen exposure a protective factor for pancreatic neuroendocrine tumours in female patients with multiple endocrine neoplasia syndrome type 1? Clin Endocrinol (Oxf). 2017;86(6):791–7. 10.1111/cen.13324. [PubMed: 28273369]
28. Khan SA, Zhao F, Goldstein LJ, et al. Early local therapy for the primary site in de novo stage iv breast cancer: results of a randomized clinical trial (EA2108). J Clin Oncol. 2022;40(9):978–87. 10.1200/JCO.21.02006. [PubMed: 34995128]
29. Stahl K, Wong W, Dodge D, et al. Benefits of surgical treatment of stage IV breast cancer for patients with known hormone receptor and HER2 status. Ann Surg Oncol. 2021;28(5):2646–58. 10.1245/s10434-020-09244-5. [PubMed: 33128117]
30. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. Ann Surg Oncol. 2018;25(11):3141–9. 10.1245/s10434-018-6494-6. [PubMed: 29777404]
31. Kayali M, Abi Jaoude J, Mohammed M, et al. Post-mastectomy radiation therapy in triple-negative breast cancer patients: analysis of the BEATRICE trial. Ann Surg Oncol. 2022;29(1):460–6. 10.1245/s10434-021-10511-2. [PubMed: 34324113]
32. Obeng-Gyasi S, Asad S, Fisher JL, Rahurkar S, Stover DG. Socioeconomic and surgical disparities are associated with rapid relapse in patients with triple-negative breast cancer. Ann Surg Oncol. 2021;28(11):6500–9. 10.1245/s10434-021-09688-3. [PubMed: 33586064]
33. Cho B, Han Y, Lian M, et al. Evaluation of racial/ethnic differences in treatment and mortality among women with triple-negative breast cancer. JAMA Oncol. 2021;7(7):1016–23. 10.1001/jamaoncol.2021.1254. [PubMed: 33983438]
34. Wang F, Shu X, Meszoely I, et al. Overall mortality after diagnosis of breast cancer in men vs women. JAMA Oncol. 2019;5(11):1589–96. 10.1001/jamaoncol.2019.2803. [PubMed: 31536134]

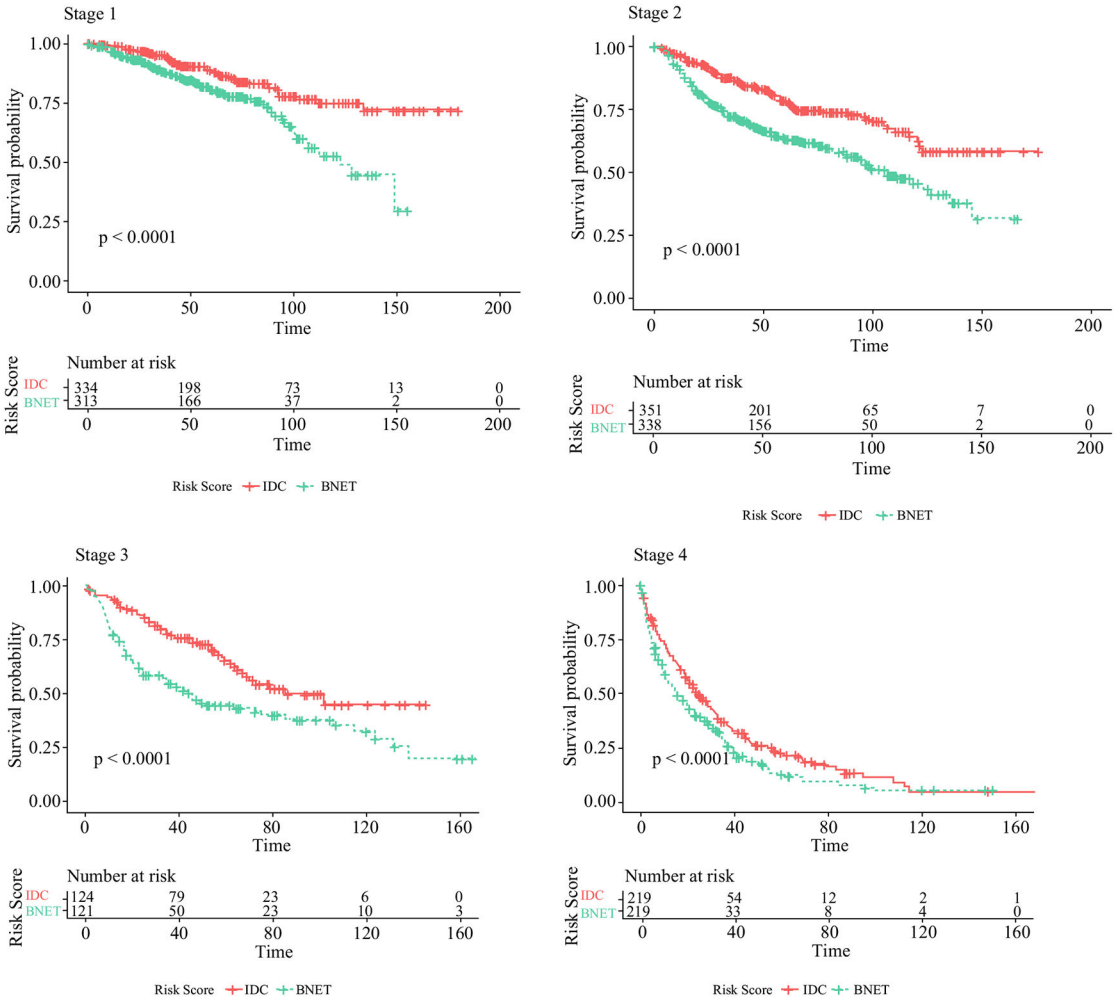

FIG. 1.

Kaplan–Meier curves comparing overall survival by disease stage for BNETs (blue) and matched IDC cohort (orange)

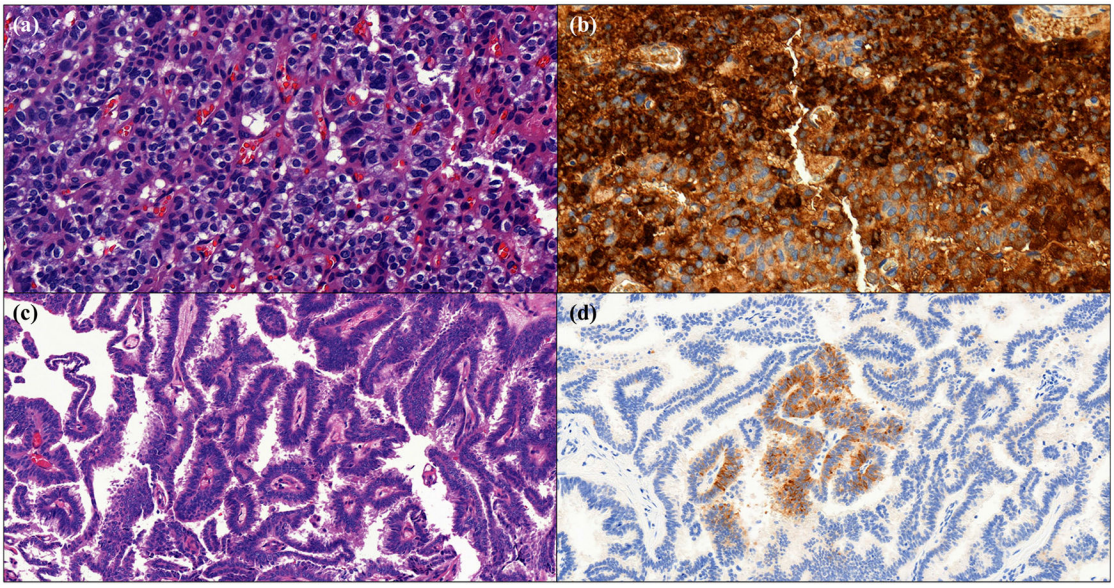

FIG. 2.

A, **B** Neuroendocrine carcinoma is the most recent classification for high-grade neuroendocrine neoplasms of the breast (per WHO 5th edition criteria) and is characterized by infiltrative nests of closely packed hyperchromatic cells with high nuclear-to-cytoplasmic ratio (**A**) (H&E, 40×) that are diffusely positive for neuroendocrine markers such as chromogranin A in this example (**B**) (IHC, 40×). **C**, **D** Encapsulated papillary carcinoma, characterized by an encapsulated tumor, papillary fronds with fibrovascular cores, and proliferation of low-grade neoplastic epithelium (**C**) (H&E, 40×), can, among other breast neoplasms, express neuroendocrine markers such synaptophysin, which is patchy positive in this example (IHC, 40×)

TABLE 1

Patient demographics and tumor characteristics by histology subtype

Variable	BNET (*N* = 1389)	IDC (*N* = 1,967,401)	*p*-Value
Age (years)			<**0.001**
<50	238 (17.1%)	436,964 (22.2%)	
50–59	316 (22.8%)	491,289 (25.0%)	
60–69	349 (25.1%)	515,368 (26.2%)	
≥ 70	486 (35.0%)	523,780 (26.6%)	
Sex assigned at birth			<**0.001**
Male	29 (2.1%)	19,669 (1.0%)	
Female	1360 (97.9%)	1,947,732 (99.0%)	
Race			0.28
Hispanic	76 (5.5%)	104,534 (5.3%)	
Non-Hispanic Black	174 (12.5%)	227,599 (11.6%)	
Non-Hispanic white	1,084 (78.0%)	1,534,083 (78.0%)	
Other	46 (3.3%)	82,807 (4.2%)	
Unknown	9 (0.6%)	18,378 (0.9%)	
CD score			<**0.001**
0	1105 (79.6%)	1,660,720 (84.4%)	
1	209 (15.0%)	239,411 (12.2%)	
≥2	75 (5.4%)	67,270 (3.4%)	
Insurance status			<**0.001**
Not insured	39 (2.8%)	40,051 (2.0%)	
Private insurance	614 (44.2%)	1,033,766 (52.5%)	
Government provided	706 (50.8%)	856,704 (43.5%)	
Unknown	30 (2.2%)	36,880 (1.9%)	
Facility location			0.15
Northeast	294 (21.2%)	384,328 (19.5%)	
South	469 (33.8%)	697,861 (35.5%)	
Midwest	331 (23.8%)	472,904 (24.0%)	
West	237 (17.1%)	308,937 (15.7%)	

Ann Surg Oncol. Author manuscript; available in PMC 2023 October 01.

Variable	BNET (*N* = 1389)	IDC (*N* = 1,967,401)	*p*-Value
Unknown	58 (4.2%)	103,371 (5.3%)	
Facility setting			0.54
Metropolitan	1178 (84.8%)	1,664,842 (84.6%)	
Urban	151 (10.9%)	223,964 (11.4%)	
Rural	24 (1.7%)	27,974 (1.4%)	
Unknown	36 (2.6%)	50,621 (2.6%)	
Facility type			**<0.001**
Community	106 (7.6%)	183,978 (9.4%)	
CCC	597 (43.0%)	856,639 (43.5%)	
Academic	459 (33.0%)	551,091 (28.0%)	
INCC	169 (12.2%)	272,322 (13.8%)	
Unknown	58 (4.2%)	103,371 (5.3%)	
Tumor size			**<0.001**
<2 cm	112 (8.1%)	187,074 (9.5%)	
2–5 cm	128 (9.2%)	99,420 (5.1%)	
>5 cm	44 (3.2%)	20,864 (1.1%)	
Unknown	1105 (79.6%)	1,660,043 (84.4%)	
Tumor grade			**<0.001**
1	128 (9.2%)	366,405 (18.6%)	
2	320 (23.0%)	770,622 (39.2%)	
3	717 (51.6%)	690,340 (35.1%)	
Unknown	224 (16.1%)	140,034 (7.1%)	
ER status			**<0.001**
ER (−)	452 (32.5%)	397,980 (20.2%)	
ER (+)	824 (59.3%)	1,489,410 (75.7%)	
Unknown	113 (8.1%)	80,011 (4.1%)	
PR status			**<0.001**
PR (−)	525 (37.8%)	581,640 (29.6%)	
PR (+)	734 (52.8%)	1,288,543 (65.5%)	
Unknown	130 (9.4%)	97,218 (4.9%)	
HER2 status			**<0.001**

Variable	BNET (*N* = 1389)	IDC (*N* = 1,967,401)	*p*-Value
HER2 (−)	815 (58.7%)	896,294 (45.6%)	
HER2 (+)	30 (2.2%)	186,236 (9.5%)	
Unknown	544 (39.2%)	884,871 (45.0%)	
Number of nodes examined			<**0.001**
0	379 (27.3%)	326,883 (16.6%)	
1–9	657 (47.3%)	1,233,609 (62.7%)	
≥ 10	274 (19.7%)	349,139 (17.7%)	
Unknown	79 (5.7%)	57,770 (2.9%)	
Nodal involvement			<**0.001**
Yes	808 (58.2%)	822,294 (41.8%)	
No	565 (40.7%)	1,130,443 (57.5%)	
Unknown	16 (1.2%)	14,664 (0.7%)	
Disease stage *			<**0.001**
1	387 (27.9%)	915,908 (46.6%)	
2	481 (34.6%)	537,178 (27.3%)	
3	169 (12.2%)	167,724 (8.5%)	
4	248 (17.9%)	72,659 (3.7%)	
Unknown	104 (7.5%)	273,932 (13.9%)	
Breast surgery type			<**0.001**
No surgery	338 (24.3%)	135,195 (6.9%)	
Lumpectomy	556 (40.0%)	1,084,960 (55.1%)	
Mastectomy	482 (34.7%)	740,524 (37.6%)	
Unknown	13 (0.9%)	6,722 (0.3%)	
Postmastectomy breast reconstruction			<**0.001**
No	395 (28.4%)	516,947 (26.3%)	
Yes	87 (6.3%)	223,577 (11.4%)	
Radiation therapy			<**0.001**
No	641 (46.1%)	855,328 (43.5%)	
Yes	635 (45.7%)	1,044,423 (53.1%)	
Unknown	113 (8.1%)	67,650 (3.4%)	
Chemotherapy			<**0.001**

Variable	BNET (*N* = 1389)	IDC (*N* = 1,967,401)	*p*-Value
No	611 (44.0%)	1,132,340 (57.6%)	
Yes	745 (53.6%)	787,235 (40.0%)	
Unknown	33 (2.4%)	47,826 (2.4%)	
Immunotherapy			<**0.001**
No	1350 (97.2%)	1,840,352 (93.5%)	
Yes	26 (1.9%)	102,657 (5.2%)	
Unknown	13 (0.9%)	24,392 (1.2%)	

Bolded *p*-value indicates that the value is statistically significant

CD Charson–Deyo, *CCC* Community Cancer Program, *INCC* Integrated Cancer Network, *ER* estrogen receptor, *PR* progesterone receptor

*AJCC 7th edition

TABLE 2

Five-year overall survival (OS) rates of patients with BNET tumors separated by disease stage along with hazard ratios (HR) and 95% confidence intervals (CI)

Disease stage	5-Year OS (%)	HR (95% CI)
Stage 1	80	1.8 (1.5–2.3)
Stage 2	63	2.0 (1.6–2.5)
Stage 3	45	1.8 (1.3–2.3)
Stage 4	13	1.5 (1.3–1.8)