Comprehensive analysis of clinicopathologic features and p53 mutation in neuroendocrine neoplasms of the breast: experience from a large academic center

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Abstract
Purpose The recent WHO classification of breast cancer (2019) categorizes breast carcinoma with neuroendocrine (NE) differentiation into three morphologically distinct subtypes: well-differentiated neuroendocrine tumor (NET), poorly differentiated neuroendocrine carcinoma (NEC), and invasive breast carcinoma, no special type with neuroendocrine differentiation (IBC-NST-NE). Data regarding the prognostic significance of neuroendocrine differentiation are conflicting and an association, if any, between p53 mutation and neuroendocrine differentiation is largely unknown.

Methods We examined p53 expression and other clinicopathologic characteristics in three types of invasive breast carcinoma with NE differentiation in a cohort of sixty-three patients, including 45 IBC-NST with NE differentiation, 10 NETs, and 8 NECs.

Results No significant difference of clinicopathologic feature was observed between IBC-NST with NE differentiation and NET, but NECs showed significantly lower expressions of hormone receptors, more mutated p53, and higher frequency of distant metastases than IBC-NST with NE differentiation and NETs.

Conclusion NECs of the breast are genetically and clinically different from IBC-NST-NEs and NETs of the breast.

Keywords Neuroendocrine neoplasm · Neuroendocrine tumor · Neuroendocrine carcinoma · p53 · Breast cancer

Introduction
Invasive breast carcinoma with neuroendocrine (NE) differentiation has been controversial in terms of its definition and clinical outcome [1–4]. The recent 5th WHO edition classified breast carcinoma with NE differentiation into three categories: (1) invasive breast carcinoma, no specific type with NE differentiation (IBC-NST-NE) (≤ 90% NE histologic features); (2) neuroendocrine tumor (NET) (well-differentiated tumor with > 90% NE histologic features); and (3) neuroendocrine carcinoma (NEC) (poorly differentiated tumor with > 90% NE histologic features) [5–7]. NET and NEC of the breast can also be combined to be called as neuroendocrine neoplasms (NENs) of the breast. The prognosis and clinicopathologic features of these tumors have been conflicting due to confusion and under-recognition of these entities [3, 8]. Additionally, p53 mutation has been frequently identified in NEC of other sites, but very little is published about p53 mutation in NEN of the breast [9, 10]. Here, we reclassified invasive breast carcinomas with neuroendocrine differentiation into three types as mentioned above based on current WHO diagnostic criteria and investigated their clinicopathologic characteristics and p53 mutation status using immunohistochemistry.

Materials and methods

Patients and specimens
After searching our pathology archives using search words “invasive breast carcinoma” and “neuroendocrine,” 63 breast carcinoma cases with NE differentiation from 2006 to 2021...
were included in this study. We reclassified these cases into IBC-NST-NE, NET, and NEC based on current WHO diagnostic criteria: IBC-NST-NEs showed NE histologic features in ≤ 90% of tumor cells except invasive solid papillary carcinoma and invasive hypercellular mucinous carcinoma; (2) NETs showed NE features in > 90% of tumor cells and low/intermediate nuclear grade; and (3) NECs showed NE features in > 90% of tumor cells, high nuclear grade, and other morphologic features, such as nuclear molding like lung NECs. For NECs with negative GATA3 and estrogen receptor (ER), clinical and radiologic information were carefully reviewed to exclude the possibility of metastatic NEC from other sites. Tumor stage, grade, metastases/recurrence status, type of treatment received, and disease status at last follow-up were collected by retrospective review of electronic medical records. Other clinicopathologic features were also collected. This study was approved by the Institutional Review Board (IRB) of the Ohio State University Wexner Medical Center.

**Immunohistochemistry**

Immunohistochemistry (IHC) was performed with antibody against synaptophysin and p53 on a Leica Bond III autostainer system (Leica Biosystems, Buffalo Grove, IL). Formalin-fixed paraffin-embedded (FFPE) tissue sections were deparaffinized/rehydrated, and antigen retrieval was performed with Bond ER2 (Leica Biosystems, equivalent to EDTA buffer, pH 8.0) at 100 °C for 20 min. Primary antibody was incubated for 30 min at room temperature and detected using the Bond Polymer Refine Detection kit (Leica Biosystems, Cat# DS9800). Tissue was then counterstained using Leica Hematoxylin as part of the Leica Bond Polymer Refine Detection kit. The mutation status of p53 was determined by p53 IHC. Wild-type p53 IHC pattern showed patchy nuclear staining in tumor cells, while mutated p53 pattern showed either diffuse strong nuclear staining or complete negative staining. Representative images from IBC-NST-NEs (1 IBC-NST-NE with wild-type p53, 1 IBC-NST-NE with mutated p53, 1 invasive solid papillary carcinoma, and 1 invasive hypercellular mucinous carcinoma), NET, and NEC are illustrated in Fig. 1.

**Statistical analysis**

Statistical analysis was performed using SAS version 9.4 for Windows (SAS Institute, Inc., Cary, NC) and GraphPad Prism (GraphPad Software, Inc. San Diego, CA). Descriptive statistics were used to summarize patients’ clinical and pathologic characteristics. Categorical data were summarized as frequency and percentage, and continuous variables as medians and ranges. Fisher’s exact test was used to compare each variable between different groups. An adjusted p value of < 0.05 was considered significant. Kaplan–Meier survival analysis was performed using GraphPad Prism.

**Results**

**Clinicopathologic features of the study cohort**

The study cohort was composed of 45 IBC-NST-NEs, 10 NETs, and 8 NECs (all were small cell carcinomas). Out of the 45 IBC-NST-NEs, there were 1 invasive solid papillary carcinoma, 2 invasive hypercellular mucinous carcinomas, 2 invasive lobular carcinomas, 1 invasive mixed ductal and lobular carcinoma, and 39 invasive ductal carcinomas, no special type. The mean age for IBC-NST-NE was 64 years, while for NET and NEC it was 61 and 59 years, respectively, and no significant difference was identified.

**Comparison between invasive carcinomas with neuroendocrine differentiation (IBC-NST-NEs) and neuroendocrine tumors of the breast (NETs)**

The only significant difference between IBC-NST-NEs and NETs was Nottingham grade, with NETs showing less grade 3 than IBC-NST-NEs. No significant difference was identified between these two groups in the examined variables, including T stage, N stage, biomarker results, p53 mutation, therapy, distant metastases, local recurrence, and overall survival (Table 1, Fig. 2). Ki-67 IHC was performed on all NETs and 10% (n = 1) showed proliferative index > 20%, 50% (n = 5) showed a proliferative index between 3 and 20%, and 40% (n = 4) had a proliferative index < 3%.

**Comparison between invasive carcinomas with neuroendocrine differentiation (IBC-NST-NEs) and neuroendocrine carcinomas of the breast (NECs)**

There was no significant difference in T and N stages between IBC-NST-NEs and NECs.

NECs were significantly associated with higher Nottingham grade (grade 3) than IBC-NST-NEs (100% vs 28.8%, p = 0.0005), but less expression of ER (12.5% vs 95.6%, p < 0.0001) and progesterone receptor (PR) (12.5% vs 77.7%, p = 0.0016). NECs showed significant association with p53-mutated IHC pattern (60% vs 11.1%, p = 0.0009). Patients with NECs were more likely treated with adjuvant therapy than patients with IBC-NST-NE. When compared to IBC-NST-NE patients, NEC patients did not show significant difference in local recurrence and survival, but they had significantly more frequent distant metastases (Table 2, Fig. 2).
Comparison between invasive carcinomas with neuroendocrine tumors and neuroendocrine carcinomas of the breast (NECs)

When compared to NETs of the breast, NECs were significantly associated with higher Nottingham grade (grade 3) (100% vs 0%, \( p = 0.0001 \)), but less expression of ER (12.5% vs 100%, \( p = 0.0005 \)) and PR (12.5% vs 70%, \( p = 0.0459 \)). NECs showed significant association with p53-mutated IHC pattern (60% vs 0%, \( p = 0.003 \)). Between these two groups, no significant difference was detected in T stage, N stage, local recurrence, and overall survival, but NEC patients had significantly more frequent distant metastases (Table 3, Fig. 2).

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**Fig. 1** Representative images of invasive breast carcinoma with neuroendocrine differentiation, neuroendocrine tumor, and neuroendocrine carcinoma of the breast. **A–C** One invasive ductal carcinoma, no other specified, with patchy neuroendocrine differentiation and wild-type p53; **D–F** One invasive ductal carcinoma, no other specified, with focal neuroendocrine differentiation and mutated p53; **G–I** One invasive solid papillary carcinoma with diffuse neuroendocrine differentiation and wild-type p53; **J–L** One invasive hypercellular mucinous carcinoma with diffuse neuroendocrine differentiation and wild-type p53; **M–O** One neuroendocrine tumor of the breast with diffuse neuroendocrine differentiation and wild-type p53; **P–R** One neuroendocrine carcinoma with diffuse neuroendocrine differentiation and mutated p53. **A, D, G, J, M, P** H&E-stained slides; **B, E, H, K, N, Q** immunostain of synaptophysin; and **C, F, I, L, O, R** immunostain of p53. Magnification: \( \times200 \)
Discussion

Although studies have suggested NENs of the breast have poorer prognosis than other invasive breast carcinomas, the findings are still controversial [8, 11–13]. For example, Tian et al. found that invasive NEC of the breast was a distinct subtype of aggressive mammary carcinoma as compared with age-, sex-, race-, tumor stage-, and HER2 status-matched IDC-NOS [14], while three other studies with 13, 12, and 7 patients, respectively, showed better prognosis in NEC of the breast [12, 15, 16]. This lack of statistically significant difference in outcome might be due to the relatively small size of the cohort and short follow-up. The other important reason for the controversial results may be due to the lack of uniform diagnostic criteria, making previous study cohorts with mixed entities. In this study, we applied current WHO diagnostic criteria to reclassify invasive carcinoma with neuroendocrine differentiation in our institution and evaluate their clinicopathologic features and prognosis. Our data have indicated that there was no significant difference of clinicopathologic feature between IBC-NST-NEs and NETs of the breast, but NECs of the breast had significantly higher frequency of distant metastases than IBC-NST-NEs and NETs, although had no statistically significant difference in overall survival, which may be caused by small sample size. Our findings are in agreement with the observations of Lavigne et al. that noted a trend of worse overall survival and progression-free survival of poorly differentiated neuroendocrine carcinomas compared with the other two groups, and these differences were not statistically significant [17].

Approximately 80% of triple-negative breast cancer (TNBC) are known to harbor \( TP53 \) gene mutations. However, the prognostic significance of the IHC-detected p53 protein expression remains controversial [18–23]. In breast cancers, p53 mutation is associated with more aggressive
Table 2  Comparison between invasive carcinoma with neuroendocrine differentiation and neuroendocrine carcinoma of the breast

| Characteristics          | IBC-NST-NE (n=45) (%) | NEC (n=8) (%) | p value |
|--------------------------|------------------------|---------------|---------|
| Age                      | 64 (38, 94)            | 59 (47, 74)   | NS      |
| Nottingham grade         |                        |               |         |
| Grade 1/2                | 32 (71.2)              | 0 (0)         | p=0.0005|
| Grade 3                  | 13 (28.8)              | 8 (100)       |         |
| T stage                  |                        |               |         |
| T1                       | 27 (60)                | 5 (62.5)      | NS      |
| T2                       | 17 (37.8)              | 2 (25)        |         |
| T3                       | 1 (2.2)                | 1 (12.5)      |         |
| N stage                  |                        |               |         |
| N0                       | 29 (64.4)              | 3 (37.5)      | NS      |
| N1                       | 13 (28.9)              | 4 (50)        |         |
| N2                       | 3 (6.7)                | 1 (12.5)      |         |
| Estrogen receptor        |                        |               |         |
| Positive                 | 43 (95.6)              | 1 (12.5)      | 0.0001  |
| Negative                 | 2 (4.4)                | 7 (87.5)      |         |
| Progesterone receptor    |                        |               |         |
| Positive                 | 35 (77.7)              | 1 (12.5)      | 0.0016  |
| Negative                 | 10 (22.3)              | 7 (87.5)      |         |
| HER 2                    |                        |               |         |
| Negative                 | 45 (100)               | 8 (100)       | NS      |
| Positive                 | 0 (0)                  | 0 (0)         |         |
| p53                      |                        |               |         |
| Wild type                | 40 (88.8)              | 2 (20)        | 0.0009  |
| Mutated                  | 5 (11.1)               | 6 (60)        |         |
| Adjuvant therapy         |                        |               |         |
| Chemotherapy             | 23 (51.0)              | 8 (100)       | 0.0018  |
| Radiation only           | 2 (4.4)                | 0 (0)         |         |
| Hormone only             | 8 (17.7)               | 0 (0)         |         |
| None                     | 8 (17.7)               | 0 (0)         |         |
| NA                       | 4 (8.8)                | 0 (0)         |         |
| Distant metastases       |                        |               |         |
| Yes                      | 8 (17.7)               | 7 (87.5)      | 0.0009  |
| No                       | 34 (75.5)              | 1 (12.5)      |         |
| NA                       | 3 (6.6)                | 0 (0.0)       |         |
| Local recurrence         |                        |               |         |
| Yes                      | 7 (15.5)               | 2 (25.0)      | NS      |
| No                       | 35 (77.7)              | 6 (75.0)      |         |
| NA                       | 3 (6.6)                | 0 (0.0)       |         |
| Survival                 |                        |               |         |
| Dead                     | 1 (2.2)                | 1 (12.5)      | NS      |
| Alive                    | 40 (89.0)              | 7 (87.5)      |         |
| NA                       | 4 (8.8)                | 0 (0.0)       |         |

IBC-NST-NE invasive breast carcinoma with neuroendocrine differentiation, NEC neuroendocrine carcinoma, NS not significant, NA not available

Table 3  Comparison between neuroendocrine tumor and neuroendocrine tumor of the breast

| Characteristics          | NET (n=10) (%) | NEC (n=8) (%) | p value |
|--------------------------|----------------|---------------|---------|
| Age                      | 61 (49, 81)   | 59 (47, 74)   | NS      |
| Nottingham grade         |                |               |         |
| Grade 1/2                | 10 (100)      | 0 (0)         | 0.0005  |
| Grade 3                  | 0 (0)         | 8 (100)       |         |
| T stage                  |                |               |         |
| T1                       | 7 (70)        | 5 (62.5)      | NS      |
| T2                       | 3 (30)        | 2 (25)        |         |
| T3                       | 0             | 1 (12.5)      |         |
| N stage                  |                |               |         |
| N0                       | 7 (70)        | 3 (37.5)      | NS      |
| N1                       | 2 (20)        | 4 (50)        |         |
| N2                       | 1 (10)        | 1 (12.5)      |         |
| Estrogen receptor        |                |               |         |
| Positive                 | 10 (100)      | 1 (12.5)      | 0.0005  |
| Negative                 | 0 (0)         | 7 (87.5)      |         |
| Progesterone receptor    |                |               |         |
| Positive                 | 7 (70)        | 1 (12.5)      | 0.0459  |
| Negative                 | 3 (30)        | 7 (87.5)      |         |
| HER 2                    |                |               |         |
| Negative                 | 9 (90)        | 8 (100)       | NS      |
| Positive                 | 1 (10)        | 0 (0)         |         |
| p53                      |                |               |         |
| Wild type                | 10 (100)      | 2 (20)        | 0.0030  |
| Mutated                  | 0 (0)         | 6 (60)        |         |
| Adjuvant therapy         |                |               |         |
| Chemotherapy             | 5 (50)        | 8 (100)       | NS      |
| Radiation only           | 1 (10)        | 0 (0)         |         |
| Hormone only             | 0 (0)         | 0 (0)         |         |
| None                     | 2 (20)        | 0 (0)         |         |
| NA                       | 2 (20)        | 0 (0)         |         |
| Distant metastases       |                |               |         |
| Yes                      | 2 (20)        | 7 (87.5)      | 0.0364  |
| No                       | 5 (50)        | 1 (12.5)      |         |
| NA                       | 3 (30)        | 0 (0.0)       |         |
| Local recurrence         |                |               |         |
| Yes                      | 0 (0)         | 2 (25.0)      | NS      |
| No                       | 9 (90)        | 6 (75.0)      |         |
| NA                       | 1 (10)        | 0 (0.0)       |         |
| Survival                 |                |               |         |
| Dead                     | 0 (0)         | 1 (12.5)      | NS      |
| Alive                    | 4 (40)        | 7 (87.5)      |         |
| NA                       | 6 (60)        | 0 (0.0)       |         |

NET neuroendocrine tumor, NEC neuroendocrine carcinoma, NS not significant, NA not available
disease and worse overall survival [20, 24]. In our study, NECs had significantly higher frequency of p53 mutation than NETs or IBC-NST-Nes (60% vs 0% or 11%). Our findings are consistent with recent studies which showed more frequent p53 mutation in NECs of the breast [10, 13].

Our study is limited by the small sample size of NETs and NECs of the breast although significant difference in several clinicopathologic variables were identified. In recognizing NETs and NECs of the breast as rare entities, multi-institutional studies with large cohorts are warranted to ascertain current results and explore potential findings. While synaptophysin staining can be seen in breast carcinomas with neuroendocrine differentiation, its expression is also common in cellular (type B) mucinous carcinomas and solid papillary carcinomas [25]. Furthermore, neuroendocrine differentiation based on IHC can be detected in up to one-third of invasive duct carcinoma, not otherwise specified (IDC-NOS) [26].

Studies reported in NETs in other organs like gastro-enteropancreatic system (GEP-NETs) reveal quite distinct characteristic molecular changes compared to IBC-NST-NEs. Molecular data on GEP-NEP are quite sporadic: gastric NECs have been shown to harbor mutation of the TP53 gene as the most recurrent alteration, affecting from 53 to 100% of cases. Loss of heterozygosity (LOH) at the TP53 and SMAD4 loci and at chromosome 6q was detected as well [27–29]. Colonic NECs are similar to colorectal adenocarcinoma, harboring recurrent mutation of APC, KRAS, Braf, and TP53, and the occurrence of microsatellite instability has been described as well. Nonetheless, they also show features of NECs from other sites, such as decreased expression of Rb and overexpression of p16 and Bcl-2 [30, 31].

In summary, this is one of the first exploratory studies to apply current WHO diagnostic criteria to reclassify invasive breast carcinomas with NE differentiation and compare clinicopathologic features among three types of these tumors, namely IBC-NST-Nes, NETs, and NECs of the breast. Out data indicated that there was no significant difference of clinicopathologic features between IBC-NST-NEs and NETs, but NECs showed significantly lower expressions of hormone receptors and higher frequency of p53 mutation and distant metastases than the other two groups, suggesting NECs are genetically and clinically different from IBC-NST-NEs and NETs.

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Declarations

Conflict of interest The authors declare that they have no financial relationship to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual patients included in the study.

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