The Clinical Significance of Neuroendocrine Features in Invasive Breast Carcinomas

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Introduction: Primary infiltrating breast carcinomas (IBCs) showing neuroendocrine (NE) differentiation comprise a heterogeneous group of tumors characterized by the presence of cytoplasmic neurosecretory granules and immunohistochemical (IHC) positivity to NE markers such as synaptophysin (SYN), chromogranin (CG), and/or CD56, and some of these also show typical cytomorphologic NE features such as presence of spindle cells, plasmacytoid cells and clear cells. In routine histologic practice, IBCs are only submitted for further IHC staining for NE markers if there are suggestive histologic features. As some tumor cells without these features may also show NE differentiation, the sensitivity and specificity of relying on these cytomorphologic features in the prediction of NE differentiation is not clearly known. Also, the clinical and prognostic significance of these cytomorphologic NE features has not been fully investigated. In this study, we evaluated the incidence of carcinoma showing IHC-defined NE differentiation and investigated the detailed cytomorphologic features, clinicopathologic parameters, and prognosis of these tumors.

Materials and methods:

Patient Data: Cases with diagnosis of IBCs were collected from Prince of Wales Hospital, Tuen Mun Hospital, and Kwong Wah Hospital in Hong Kong from 2002 to 2009. Demographics and prognostic data were obtained from medical records. *Tissue Microarray Construction and IHC Staining:* IHC staining for NE markers SYN, CG and CD56 was performed on TMA cores. The staining intensity and percentage of stained cells were evaluated. Cases showing NE differentiation were then classified into low (1%–49%) and high (≥50%) expression. Data for hormonal and other IHC markers were retrieved from our database. The tumors were also classified into the five different molecular subtypes using IHC surrogates.

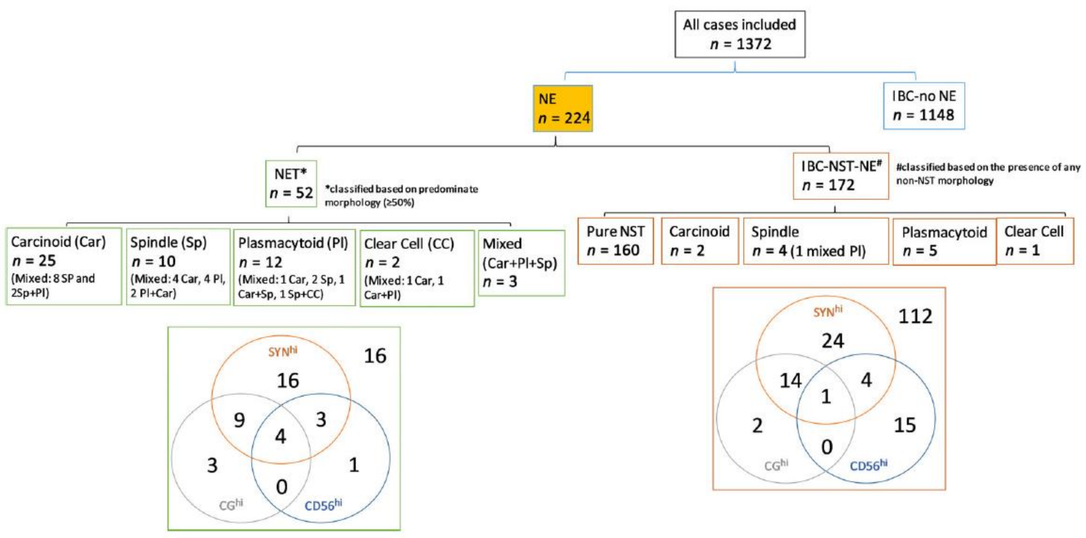
Further NE Differentiation Assessment: The histologic features were assessed, and IHC staining of NE markers (SYN, CG, and CD56) was repeated in the corresponding full sections. Histologically, the tumors were evaluated for cytomorphologic NE features (morphologic features of carcinoid, plasmacytoid, spindled, clear cell, and small cell) and the percentage of tumor area occupied by these tumor cells. All the IBCs with NE features were classified into three groups: (a) NET, well differentiated, which showed ≥90% cytomorphologic NE features; (b) NEC, poorly differentiated or small cell carcinoma with cytomorphologic features resembling small cell lung cancers; and (c) IBC-NST-NE, where some (10%–90%) tumor cells showed NE differentiation, as determined by NE morphological features and/or NE marker expression.

Statistical Analysis: Statistical analysis was performed using SPSS Version 23.0. Data. The Mann-Whitney-Wilcoxon test, χ^2, and Fisher's exact test were used, as appropriate, to identify differences between the two groups. Survival was analyzed using Kaplan-Meier method and compared statistically using log-rank test. Univariate and multivariate cox regression analyses were used for identifying Prognostic factors. The p values were two-tailed, and the level of significance was taken as <.05.

Results:

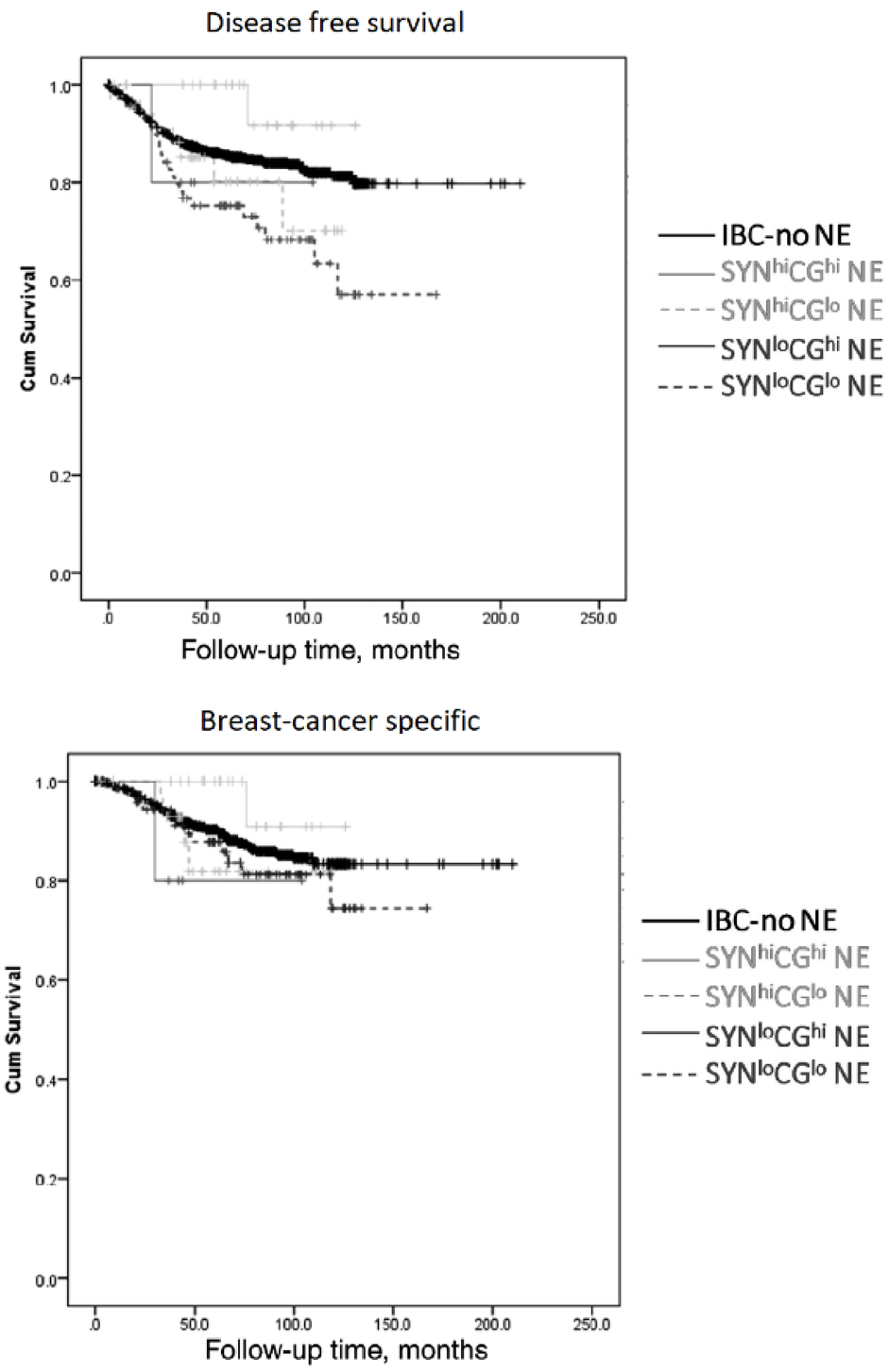
Incidence: The calculated incidence of IBC with NE differentiation was 16.3% in our study, of which 23.2% were NET, and the remaining 76.8% were IBC-NST-NE. There were no NEC cases in this cohort

Neuroendocrine Marker Expression: The distribution of cases included in the study is presented in the figure below:



Comparison Between NET, IBC-NST-NE, and Breast Carcinomas Without NE Differentiation: NET and IBC-NST-NE were similarly associated with positive estrogen receptor expression and lower grade compared to IBC-no NE ($p < .001$). IBC-NST-NE, but not NET, demonstrated significantly worse survival than the IBC-non NE cases.

NE Expression and Patient Outcome: Based on high (≥50%) and low (<50%) expression for each NE marker, independent poor disease-free survival for SYN^{lo} CG^{lo} and SYN^{hi} CG^{lo} cancers was found.



NE Markers: SYN and CG expression correlated with each other and they shared similar clinicopathologic characteristics; but not with CD56. In addition, CD56-only positive cases were associated with hormone receptors negativity and basal markers positivity ($p \leq .019$), and patients' outcome was similar to IBC-non NE cancers.

Conclusions:

Our study showed that IBCs with NE differentiation occurred in older patients and were associated with lower histologic grade, compared with IBC–no NE, regardless of their cytomorphologic types. In addition, IBCs with NE differentiation were more commonly luminal but with a poorer DFS. In contrast, NET were associated with lower grade, pN and pT stages, and Ki-67 expression and showed similar DFS as IBC-no NE and a trend of better outcome when compared with IBC-NST-NE which showed a shorter DFS when compared with IBC-NE. These results suggested a potential value in stratifying IBCs with NE differentiation into low expression group (mostly IBC-NST-NE) with worse outcome and a high expression group (mostly NET or tumors with special cytomorphologic NE features) with better outcome. The current study also demonstrated a high sensitivity for SYN. For CG, although having a lower sensitivity, its expression may have direct bearing on outcome, as CG^{lo} status defined cases with worst survival. In addition, we found that CD56-only positive carcinomas showed a different clinicopathologic and biomarker expression profile behave more like IBC–no NE. It is not clear if CD56 could be truly a biologically meaningful NE marker.

References:

World Health Organization. WHO classification of tumours of the Breast. 5th ed. Lyon: IARC; 2019.