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Original contribution

Prognostic significance of tumor grading and staging in mammary carcinomas with neuroendocrine differentiation☆,☆☆

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Summary Invasive mammary carcinoma with neuroendocrine differentiation has been controversial in terms of its definition and clinical outcome. In 2003, the World Health Organization histologic classification of tumors designated this entity as neuroendocrine carcinoma of the breast and defined mammary neuroendocrine carcinoma as expression of neuroendocrine markers in more than 50% of tumor cells. It is an uncommon neoplasm. Our recent study showed that it is a unique clinicopathologic entity and has a poor clinical outcome compared with invasive mammary carcinoma with similar pathologic stage. Other investigators have also demonstrated a different molecular profile in this type of tumor from that of invasive ductal carcinoma. It is unknown whether the current prognostic markers for invasive mammary carcinoma are also applicable for neuroendocrine carcinoma of the breast. In the current study, we reviewed the clinicopathologic features and outcome data in 74 cases of mammary neuroendocrine carcinoma from the surgical pathology files at The University of Texas, MD Anderson Cancer Center, to identify relevant prognostic markers for this tumor type. As shown previously by univariate analysis, large tumor size, high nuclear grade, and presence of regional lymph node metastasis are adverse prognostic factors for overall survival and distant recurrence–free survival. In the current study, multivariate analysis revealed that overall survival was predicted by tumor size, lymph node status, and proliferation rate as judged by Ki-67 immunohistochemistry. Only nodal status proved

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to be a significant independent prognostic factor for distant recurrence–free survival. Neither mitosis score nor histologic grade predicted survival in mammary neuroendocrine carcinoma. Our data suggest that routine evaluation of Ki-67 proliferation index in these unusual tumors may provide more valuable information than mitotic count alone.

1. Introduction

Primary invasive mammary carcinoma with neuroendocrine (NE) differentiation was described more than 4 decades ago [1]. However, the terminology, definition, and clinical outcome of NE differentiation in breast cancer have been controversial. The terminology of NE carcinoma (NEC) of the breast was proposed in the 2003 World Health Organization (WHO) histologic classification of tumors of the breast and female genital organs, which defined it as mammary carcinoma with more than 50% of neoplastic cells expressing NE markers by immunohistochemistry [2].

Most publications on breast carcinomas with NE differentiation were dated before the 2003 WHO classification [1,3-10]. There have been only 6 publications using the new WHO criteria, but most of those studies were conducted on small case numbers, and prognostic information were limited [10-15]. We recently conducted a case-control study of invasive mammary carcinomas that met the WHO criteria for classification as NECs (ie, appropriate morphologic features and labeling for NE markers in >50% of the tumor) [16]. In that study, we compared invasive mammary NEC with invasive ductal carcinoma, not otherwise specified (IDC, NOS) after matching for age, sex, race, tumor stage, and HER2/neu status. We showed that invasive mammary NEC is an aggressive tumor, with a higher tendency for local and distant recurrence and poorer overall survival (OS) than IDC, NOS. In addition, our data demonstrated that NE differentiation is an adverse prognostic factor independent of estrogen and progesterone receptor (ER/PR) status and nuclear grade. In our population, NECs were treated similarly to IDC, NOS, but they failed to respond as well to conventional therapies for breast cancer including hormonal manipulation, chemotherapy, and radiation.

Prognostic markers for ductal and lobular carcinomas of the breast, NOS, have been well clarified, and several well-standardized grading and staging systems have been used for breast carcinoma in recent years. In the commonly used Nottingham system, for example, tumor grade is assigned by a combination of mitotic rate, gland formation, and nuclear grade [17], with higher tumor grade reflecting a poorer prognosis. Presence of lymphovascular invasion, loss of ER/PR expression, Her-2/neu amplification, greater tumor size, and regional lymph node metastasis are also all poor prognostic features in mammary carcinoma, NOS. It is unknown, however, whether these features or others serve as prognostic markers in mammary NEC. In this study, we demonstrate that tumor size, axillary lymph node status, lymphovascular invasion, and proliferation rate by Ki67 immunostaining—but not nuclear grade or Nottingham histologic grade—are significant predictors of OS and/or distant recurrence–free survival (DRFS) in NEC of the breast.

2. Materials and methods

2.1. Study population and histologic review

Primary and metastatic invasive NECs of the breast were retrieved from the surgical pathology files of the University of Texas, MD Anderson Cancer Center (MDACC). The study population comprised 74 patients whose original diagnoses of invasive breast cancer were made between January 1984 and August 2008. All cases were confirmed to be NEC by immunohistochemical staining (ie, >50% of the invasive tumor cells expressing synaptophysin and/or chromogranin A based on the current WHO criteria). Details about the clinical features and acquisition of the study population have been recently published [16].

Cases with variable morphology were included in the study as long as they fulfilled the WHO diagnostic criteria: (1) with histologic features similar to NE tumors in the gastrointestinal tract and lung and (2) with more than 50% of the tumor cells expressed NE markers by immunohistochemistry. The following cases were excluded: (1) tumors with only focal (<50%) NE differentiation in the invasive cells, (2) tumors with a significant (>25%) in situ component, (3) small cell carcinomas, and (4) metastatic NECs from other organs based on clinical history in conjunction with pathologic evaluation. Our companion study of the same group of NEC cases showed that the histologic patterns were often mixed within the tumor. Papillary and nesting pattern were the most common patterns in mammary NEC; other patterns included cellular mucinous, trabecular/gyriform, and micropapillary; IDC, NOS pattern was seen admixed with other patterns characteristic of NE tumors in 18% of our cases [18]. Fig. 1 shows an example of the histolomorphology as well as the immunohistochemical confirmation of NE differentiation.

Hematoxylin and eosin–stained slides were reviewed for nuclear grade, mitotic rate, histologic grade (combined assessment of tubule/gland formation, nuclear pleomorphism, and mitotic count), presence of lymphovascular invasion, and mucinous differentiation. Nuclear grade and