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Clinical, Pathologic, and Biologic Characterization of WHO Grade 3, Non Small Cell and Non Large Cell Neuroendocrine Carcinoma of the Pancreas

Chanjuan Shi[1]; Jesse Wright[2]; Frank Revetta[1]; Eric Liu[2]; Alex Parikh[2]; Kay Washington[1]; Nipun Merchant[2,3]

[1]From the Department of Pathology, Vanderbilt University Medical Center, Nashville, TN 37232
[2]From the Department of Surgery, Vanderbilt University Medical Center, Nashville, TN 37232
[3]From the Department of Cancer Biology, Vanderbilt University Medical Center, Nashville, TN 37232

Background: WHO has classified pancreatic neuroendocrine tumors (PanNETs) into 3 grades based on Ki-67 and mitosis: grade 1 (Ki-67≤2% and mitosis<2/10 HPF), grade 2 (Ki-67=3-20% and/or mitosis=2-20/10 HPF), and grade 3 (Ki-67>20% and/or mitosis>20/10 HPF). Little is known about a small percentage of grade 3 PanNETs that have a morphology indistinct from grade 1-2 PanNETs, but with a Ki-67>20% and/or mitosis>20/10 HPF. This study explores their clinical, pathologic and biological features.

Methods: Review of 94 resected PanNET patients from 2002 to 2011 identified 10 WHO grade 3 PanNETs that were neither small cell carcinoma nor large cell NET. These tumors had morphology very similar to grade 1-2 PanNETs, but had mitosis >20/10 HPF (n=5) and/or a Ki-67>20% (n=10). Clinical history and pathologic features were reviewed. Specimens were immunohistochemically labeled with Ki67, her2/neu, c-Met, and EGFR.

Results: Of the 10 cases, 60% were male and ages ranged from 38 - 78 years. 3 pts had a hereditary syndrome: 2 with MEN1 and 1 with Von Hippel–Lindau. Tumor size ranged from 2.4 to 26.0 cm. 5 pts presented with stage IV disease, 4 with stage II and 1 with stage I. Overall survival for these pts was significantly worse than that of grade 1 and 2 PanNET pts. Focal necrosis, lymphovascular invasion (LVI), and perineural invasion (PNI) were observed in 50%, 70%, and 30% of cases, respectively. All cases were diffusely and strongly labeled with c-Met; 6 had weak Her2/neu membranous labeling and 4 had expression of EGFR.

Conclusion: Grade 3 PanNETs account for ~10% of PanNETs and can occur in pts with or without a hereditary syndrome. Most pts present with advanced disease and have worse prognosis. The tumors are always associated with high risk pathologic features (necrosis, LVI, PNI, and thickened fibrotic septa) and express other growth factor receptors such as c-Met, Her2/neu or EGFR, which may provide a clue towards further understanding their biology to identify novel targeted therapies.