C-33

High-Grade Pancreatic Neuroendocrine Neoplasms: Interobserver Diagnostic Accuracy and Relationship with Clinicopathological and Molecular Characteristics

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BACKGROUND

The pathogenesis, biologic behavior, and treatment of well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC) are different. The diagnosis relies on multiple factors, but pathologic assessment is crucial. Based on currently available diagnostic criteria, the distinction between NET G3 and NEC are made on morphologic assessment, without taking Ki-67 proliferative index into consideration. This study looks at the concordance rates among experienced gastrointestinal pathologists following published guidelines (current WHO criteria and additional morphologic criteria based on a recent international consensus study) and how it compares to clinical parameter-based retrospective categorization.

METHODS

32 cases of NET G3 and NEC were selected from a retrospective search of cases for pancreatic neuroendocrine neoplasms, with tumor slide availability in-house, including Ki-67 stain. A morphologic review was performed by 8 GI pathologists (blinded to all other information, including proliferative indices), practicing at a tertiary cancer center for a median of 20 years. A "clinical" diagnosis was separately formulated based on information collected from electronic medical records focusing on special imaging results (octreotide/ gallium scan, FDG-PET), molecular data (if available), and clinical course of the disease, including survival and response to treatment received. Reliability assessment and correlations were studied using standard statistical software.

RESULTS

The cases evaluated by all eight pathologists and showed only a fair interobserver agreement on diagnosis (kappa (κ)= 0.334). There was a majority agreement of ≥ 5/8 pathologists on 30 (90.1%) cases. The most discordant case (only 2/8 observers agreed with the clinical diagnosis) demonstrated some morphologic features similar to NEC. The highest consensus on morphologic criteria was noted for the absence or presence of geographic necrosis (κ=0.497 moderate).

The "clinical" diagnosis formulated based on multiple clinical parameters correlated strongly with overall survival (2071+/- 13 days for NET and 720 +/- 386 days for NEC; p=0.006) as well as Ki-67 proliferative index (33 +/- 17 for NET and 53 +/- 22 for NEC; p=0.01). Ki-67 proliferative index also independently showed negative correlation with survival (p=0.027).

CONCLUSIONS

The distinction between NET G3 and NEC solely based on morphology, as is the current recommendation, is challenging, especially in a small biopsy. Ancillary studies (immunohistochemistry and/or molecular studies) and correlation with clinical datapoints such as special imaging (octreotide, 68-Gallium DOTATATE, and/or FDG PET) and clinical course and tumor response to therapy is probably warranted.

ABSTRACT ID 21411