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Clinical and Immunohistochemical Features of Non-Pancreatic Gastrointestinal Neuroendocrine Neoplasms

Allison J Zemek[1]; Michael A DiMaio[1]; John Allen[2]; Hemamalini Vairamuthu[2]; Raymond R Balise[2]; Teri A Longacre[1] ; Pamela L Kunz[2]

[1]Department of Pathology, Stanford University Medical Center, Stanford, CA 94305
[2]Department of Medicine, Division of Oncology, Stanford University Medical Center, Stanford, CA 94305

Background: Non-pancreatic gastrointestinal neuroendocrine neoplasms are classified in the WHO 2010 system into three grades, using mitotic figure counts and Ki-67 indices. There is increasing evidence that immunohistochemical expression of p16 and p53; and/or loss of chromogranin may provide additional prognostic information predicting worse clinical outcome.

Methods: Non-pancreatic gastrointestinal neuroendocrine neoplasms were identified in a retrospective search of the surgical pathology database of a large academic medical center from 1992-2013, and compiled in a tissue microarray. H&E and Ki67-stained sections were examined to classify the lesions as well-differentiated neuroendocrine tumors, including WHO grades 1 and 2 (WDNET), versus poorly-differentiated neuroendocrine carcinoma, WHO grade 3 (PDNEC). Immunohistochemistry for p16, p53 and chromogranin was performed. Kaplan-Meier analysis was used to calculate overall survival (OS). Cox proportional hazards models were constructed to assess significance of differentiation, p16, p53 and chromogranin with survival.

Results: 178 non-pancreatic gastrointestinal neuroendocrine neoplasms were identified. Median age was 58.5 years, 94 (53%) were female, 169 (95%) were WDNETs, 9 (5%) were PDNETs. The majority of cases were p16/p53 negative and chromogranin positive. The 5-year OS rate for the entire cohort was 75%. Of the PDNECs, p16/53 positive cases had worse OS. Univariate Cox regression analysis demonstrated that PDNEC was associated with an increased hazard of death with a HR of 18.1 ($p<0.0001$), as was p53 expression with a HR of 8.6 ($p<0.0001$). However, only poor differentiation (PDNEC) maintained this association by bivariate COX analysis ($p<0.001$).

Conclusion: In a population of non-pancreatic gastrointestinal neuroendocrine neoplasms, patients were predominantly young, female, and had WDNETs. As expected, PDNEC had poorer OS compared to WDNET. Of PDNEC, p16/53 positive cases had poorer OS compared to p16/53 negative cases. In univariate Cox regression analysis, both PDNEC and p53 expression were associated with increased hazard of death. In bivariate Cox analysis, only PDNEC maintained this association. Our analysis was limited by low case numbers for PDNEC and p16/53 expression. Further studies are needed to determine if p16, p53 and chromogranin may aid grading of neuroendocrine neoplasms.