A comparison of the WHO 2004 and 2010 classification systems in pancreatic neuroendocrine tumors (Pancreatic NET)

Department of Pathology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

ABSTRACT
Pancreatic NETs are rare tumors with multiple classification systems. Previous classification systems included tumor size, histologic grade, mitoses, and metastases. The current WHO 2010 system utilizes mitotic rate and Ki67 to assign a grade. We compared the WHO 2004 and 2010 classification systems in predicting mortality and metastasis.

Pancreatic NETs were used to classify 50 cases of Pancreatic NET according to the WHO 2004 and WHO 2010 grading systems. The WHO 2010 grading was investigated using an exact chi squared test. WHO 2010 grade was assigned by reviewing the entire slide at >20X magnification. The relationship between the WHO 2004 and WHO 2010 grading system was explored using a logistic regression test. Survival was explored using Cox Proportional Hazards regression test. There was a significant difference in survival by tumor size, histologic grade, Ki67, mitoses, perineural and lymphovascular invasion, lymph node and distant metastases.

METHODS
We conducted a retrospective review of 50 patients with Pancreatic NET diagnosed and treated at Thomas Jefferson University Hospital between the years of 2000 and 2010. Pathologic parameters were reviewed including tumor size, histologic grade, Ki67, mitoses, perineural and lymphovascular invasion, lymph node and distant metastases. These parameters were used to grade each case according to the WHO 2004 and WHO 2010 grading system. The relationship between the WHO 2004 and WHO 2010 grading system was explored using an exact Chi squared test. WHO 2004 categorization was next explored by vital status, by the exact method, in order to determine if there was a difference in survivorship and metastasis by grading system. Associations between death and categorical variables were tested using exact methods and between death and continuous variables by the Wilcoxon test.

RESULTS
Table 1 presents the summary of patient and disease characteristics. Patients were mostly female (62%) and had an average age of 60; over half had a cardiovascular comorbidity. Figure 1 presents the relationship between WHO grades 2004 and 2010. The WHO grades are significantly associated with one another (p < 0.001). In Table 2, both grading systems were strongly associated with predicting mortality, all cases of mortality were in the higher grades: PDEC and WDEC for 2004 and G2, and G3 for 2010. Table 3 presents similar results with regard to metastasis. Again there are significant associations: however the 2010 grades does slightly better in that metastases occur only in higher grades (G2 and G3). This is a moderate difference in terms of associations. Comorbidities and tumor characteristics were considered as well and were not significantly different by mortality, patients with lymphovascular or perineural invasion had significantly higher mortality.

CONCLUSION
This WHO 2010 grading system is strongly associated with predicting mortality and performs better in predicting liver metastasis than the 2004 grading system. Future studies include determining which tumors responded best to chemotherapy following surgery as well as finding molecular markers that correlate with tumor grade and prognosis.

INTRODUCTION
Pancreatic neuroendocrine tumors are rare tumors of the pancreas that are believed to develop from pluripotent ductal cells with the ability to differentiate along neuroendocrine lines. Approximately 80% of these tumors occur as part of inherited disorders including Multiple Endocrine Neoplasia type 1 (MEN1), von Hippel-Lindau disease (VHL), neurofibromatosis 1 (NF-1), and von Recklinghausen disease (VHL). Mitotic rate and Ki67 index are important in grading these tumors.

METHODOLOGY
Histologic samples from 50 patients were reviewed and graded using both the WHO 2004 and WHO 2010 grading systems. The WHO 2004 grading was evaluated using an exact chi squared test. WHO 2004 categorization was next explored by vital status, by the exact method, in order to determine if there was a difference in survivorship and metastasis by grading system. Associations between death and categorical variables were tested using exact methods and between death and continuous variables by the Wilcoxon test. Survival was explored using Cox proportional hazards regression test (Cox).

REFERENCES