Correlation of Mitotic Index and Ki-67 And Their Impacts on Survival of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) at Ramathibodi Hospital

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Background: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are the most prevalent type of neuroendocrine tumors although limited data is available on GEP-NET in Thai patients. Proliferative index as determined by mitotic rate/index (MI) and Ki-67 labelling index have proven to be a strong prognostic factor in GEP-NETs and many experts have recommended that both markers be performed in all cases although this is not accepted universally. Therefore, this study aimed to explore the agreement of these 2 methods and their correlation with survival in our center.

Method: Records of GEP-NETs patients in Ramathibodi hospital between January 2007 and December 2011 were retrospectively reviewed. Demographic and clinical data together with treatment and outcome (recurrence and overall survival) were collected. A pathologist blinded to clinical outcome reviewed the MI and Ki-67 index in all cases. Concordancy of the 2 methods and correlation with survival were analyzed. Prognostic factors were tested in univariate and multivariate fashion.

Results: A total of 46 cases of GEP-NETs were analyzed. The most common primary tumor site was pancreas (39.1%) and only 9% were functional tumor. Nearly half presented with stage IV (45.7%). Over two-thirds had surgery as part of initial treatment. The median overall survival has not been reached. The 1, 2, and 5-year overall survival rates were 75%, 70% and 66%, respectively. Both MI and Ki-67 were analyzed in 26 patients with concordant rate of the 2 methods of 65.4% and $\kappa$ value of 0.46. Grading of tumors using combined MI and Ki-67 index according to WHO guideline resulted in more patients being upgraded to higher level than using MI alone. Univariate analysis revealed that gender, stage, surgery, chemotherapy, MI, WHO tumor grade (and not Ki-67) and relapse/progression were significantly associated with survival in univariate analysis. Only surgery remained an independent factor of prognosis in a multivariate analysis (excluding mitotic and Ki-67 index due to small sample size). After adjusting for presence of surgery, both mitotic and Ki-67 indices maintained their prognostic value as determined by comparison of ROC areas (0.93 and 0.79, respectively, $p$ 0.11).

Conclusion: In this preliminary analysis, WHO classification of GEP-NETs, based on either mitosis index or Ki-67 index, correlated with survival. Both indices had concordancy in a moderate agreement level. Both markers of proliferation are inversely correlated with survival and can be analyzed independently for assignment of grade.