The Role of Insulin in Tumor Recurrence after Resection of Pancreatic Malignancy. Results of a Prospective Study

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Context Recent findings suggest that insulin levels and insulin resistance are related to the prognosis of patients with different malignancies. **Objectives** To evaluate the role of insulin in tumor recurrence after resection of pancreatic malignancies. **Methods** From January 2008 to October 2012, 351 patients with pancreatic malignancy (198 ductal carcinoma, 35 other periampullary adenocarcinoma, 42 neuroendocrine tumors, 45 pancreatic cystic neoplasms and 31 other tumors) underwent resection and were enrolled in a prospective observational study. Clinical and biochemical data (including fasting blood glucose, insulin and C-peptide) were collected. Insulin resistance was evaluated using HOMA2-IR model. Follow-up data were collected one month after discharge and every six months thereafter. Logistic and Cox regression analysis were used when appropriate. Multivariate analysis was performed using variables significant at univariate analysis. Overall survival and disease-free survival were estimated according to Kaplan-Meier. **Results** Median follow-up time was 764±35 days. Median disease-free survival was 469±29 days and median overall survival 685±59 days. Relapse occurred in 165 of 351 patients (47.0%), 150 of whom died (42.7%). Based on serum insulin levels, patients were divided into tertiles: median survival was 786±145 days, 680±83 days and 520±88 days for first (24.1±9.2 pmol/L), second (50.1±7.8 pmol/L) and third (127±97 pmol/L) tertile, respectively (P=0.042, III *vs.* I and II pooled together). Cox regression analysis for overall survival showed that older age, higher serum insulin levels (OR=1.024, 95% CI: 1.002-1.047; P=0.032], higher insulin resistance (OR=1.105, 95% CI: 1.003-1.217; 0.043), pN1, G3 and R1 were strongly associated with lower survival. The multivariate analysis confirmed older age and G3 as independent predictors of overall survival. Univariate analysis for predictors of metastatic recurrence found that higher serum insulin levels, diagnosis of ductal carcinoma, pT, pN1, G and R1 were significant factors. Multivariate analysis confirmed that higher insulin level (OR=1.030, 95% CI: 1.001-1.060; P=0.043) and grading (OR=1.656, 95% CI: 1.17-2.3; P=0.004) were independent predictors of metastases. **Conclusions** Hyper-insulinemia is strongly associated with metastatic recurrence after resection of pancreatic malignancies.