C-46

Alternative Lengthening of Telomeres Is Associated with Aggressive Pathologic Features and Increased Recurrence Risk in Large Pancreatic Neuroendocrine Tumors

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BACKGROUND: The behavior of pancreatic neuroendocrine tumors (pNETs) ranges from indolent to aggressive. The decision to observe or resect a pNET is primarily based on size, but size is an imperfect indicator of tumor aggressiveness. Recently, alternative lengthening of telomeres (ALT) has emerged as a promising marker of aggressive behavior in pNETs.

METHODS: Patients with well-differentiated non-functional sporadic pNETs >3 cm in size who underwent resection at Mayo Clinic from 2000 to 2019 were identified and clinical data obtained from medical records. ALT status was assessed by fluorescence in situ hybridization (FISH). Patients were classified as low-risk if they had both Ki-67 <3% and were ALT-negative or high-risk if they had either Ki-67 >3% or were ALT-positive.

RESULTS: Of 82 patients identified, 42 (51.2%) were ALT-positive and 40 (48.8%) ALT-negative. ALT-positivity was associated with larger tumor size (50 vs. 41 mm, p=0.010), higher Ki-67 index (82.6% vs. 40.0% >3%, p=0.018), and lymphovascular invasion (LVI) (56.7% vs. 18.8%, p=0.031). ALT-positive patients had worse recurrence-free survival (RFS) (p=0.002) but not overall survival (p=0.362). In univariate analysis, ALT (HR 3.78, p=0.003), LVI (HR 4.94, p=0.005), and perineural invasion (PNI) (HR 22.99, p=0.003) were associated with recurrence. In multivariate analysis, only Ki-67 index >3% (HR 14.61, p=0.009) and PNI (HR 7.03, p=0.001) remained significant predictors of recurrence. Patients who had both Ki-67 and ALT data available were stratified into low-risk (n=9) or high-risk (n=29) groups. RFS was significantly different between the two groups (p=0.049), with a

5-year RFS of 100.0% in the low-risk group and 43.3% in the high-risk group.

CONCLUSION: ALT is associated with aggressive pathologic features and worse RFS in large resected pNETs. Combined use of Ki-67 and ALT status could improve recurrence risk stratification following resection and potentially improve treatment selection for patients who are candidates for both observation and resection.

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