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Correlation of Smad4 Status With Outcomes in Patients Receiving Erlotinib Combined With Adjuvant Chemoradiation and Chemotherapy After Resection for Pancreatic Adenocarcinoma

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Introduction

Although adjuvant therapy may reduce the risk of local and distant recurrence, it remains unclear why some patients experience widely disseminated disease whereas others experience recurrence only locally or not at all. Identification of biomarker predictors for local and distant recurrence could guide the administration of targeted therapies in the adjuvant setting. A potential prognostic biomarker is the tumor-suppressor gene *DPC4(SMAD4)* (1). *DPC4* encodes the Smad4 protein, which functions as a central mediator of the canonical transforming growth factor (TGF)-β signaling pathway involved in cell proliferation, differentiation, apoptosis, and migration. The significance of Smad4 in pancreatic ductal adenocarcinoma (PDAC), and hence TGF-β signaling, is exemplified by its inactivation in approximately 55% of PDAC cases (2). Previous studies have suggested that immunolabeling for the Smad4 protein or genetic mutation/deletion status of the *DPC4* gene influences overall survival (OS) after tumor resection (3).

In an autopsy series of patients with advanced PDAC, those whose tumors had intact Smad4 were more likely to die of localized disease, whereas patients whose tumor did not express

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Smad4 were more likely to die of metastatic disease (2). However, because the autopsy specimens were mostly from patients with advanced PDAC, it remains unclear whether Smad4 status influences patterns of failure in resectable PDAC patients receiving adjuvant chemoradiation (CRT). Therefore, we evaluated whether Smad4 expression, as determined by immunolabeling, predicts for survival and patterns of failure after erlotinib-based adjuvant CRT.

Methods and Materials

Smad4 status was determined by immunolabeling of the resected specimen and was graded as either intact or lost by a single pathologist (C.I.D.), who was blinded to patient outcome or pattern of failure as previously described (2).

Results

Of the 48 patients, 29 (60.4%) had available tumor specimens for Smad4 immunolabeling. Smad4 was intact in 15 (52%) and lost in 14 (48%) specimens. OS was 24.4 months versus 18.3 months in patients with intact Smad4 status versus those with loss of Smad4 ($P = .308$). Recurrence-free survival was significantly longer (17.4 months) in patients with intact Smad4 status than in those with loss of Smad4 (11.5 months, $P = .003$).

Discussion

The *DPC4(SMAD4)* gene has been identified as 1 of the 4 frequently mutated genes in PDAC. In our study, recurrence-free survival was inferior in those with loss of Smad4 ($P = .003$); however, Smad4 status was not associated with OS. These findings are also consistent with those reported by Crane and colleagues (4) in patients with locally advanced pancreatic cancer who received cetuximab-based CRT. Radiation Therapy Oncology Group 1201 will further elucidate the role of Smad4 status (cytology specimens) in patients with locally advanced pancreatic cancer.

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