Aim: Activating KRAS mutations are the major driver gene aberrations of pancreatic cancer and are present in over 90% of patients with pancreatic cancer. On the other hand, aberrations of the CDKN2A, TP53, and SMAD4 genes are also frequent events in pancreatic carcinogenesis. We constructed a mutation profile of pancreatic cancer-associated genes. Additionally, we analyzed the relationship between gene mutations and clinicopathological factors.

Methods: Genomic DNA samples were extracted from fresh frozen surgical specimens obtained from 100 patients (98 with pancreatic ductal adenocarcinoma, 2 with adenosquamous carcinoma) who underwent radical operations for pancreatic cancer at the National Cancer Center Hospital between March 2005 and June 2012. Next-generation sequencer-based targeted deep sequencing was performed using a Cancer Panel reagent that covers representative cancer-related genes (50 genes, 190 hot spots).

Results: Mutations were detected in 97% of the cases, and the average number of mutations per tumor sample was 1.6. The most frequently mutated genes were KRAS (96%), TP53 (42%), SMAD4 (13%), and CDKN2A (7%). The most common mutation types of KRAS were G12D (48%), G12V (32%), and G12R (10%) in our cohort. The known druggable mutations that were detected were GNAS (1%), PIK3CA (1%), and KIT (1%). Among the patients who underwent radical operations followed by adjuvant chemotherapy (71 patients), the survival of patients who had 0 to 2 mutations in the 4 major driver genes (KRAS, TP53, SMAD4, and CDKN2A) was significantly longer than that of patients who had 3 or more mutations (median overall survival, 40.0 months vs. 12.6 months, P = 0.0020). A multivariate Cox proportional hazard model analysis showed that a low number of mutations among these 4 genes was significantly associated with a better prognosis.

Conclusions: KRAS, TP53, SMAD4, and CDKN2A were the most frequently mutated genes in Japanese patients with pancreatic cancer. The number of mutations among these 4 genes as detected using targeted deep sequencing may be a useful biomarker for the prediction of postoperative outcomes.

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