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Early Detection of Pancreatic Cancer in Patients With Chronic Liver Disease Under Hepatocellular Carcinoma Surveillance

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Abstract

Objective: To evaluate whether patients with hepatitis B virus (HBV)− and hepatitis C virus (HCV)−related chronic liver disease were diagnosed as having pancreatic cancer (PC) at an early stage during abdominal imaging surveillance for hepatocellular carcinoma (HCC).

Patients and Methods: We retrospectively examined 447 patients with PC diagnosed at Ehime University Hospital and affiliated centers (2011-2013). Data were collected regarding HBV and HCV status, likelihood of PC diagnosis, and Union for International Cancer Control (UICC) stage. Intergroup comparisons were performed using the χ^2 test.

Results: The UICC stage distribution in the HCC surveillance group (n=16) was stage 0 (n=2, 12.5%), stage IA (n=3, 18.8%), stage IB (n=2, 12.5%), stage IIA (n=2, 12.5%), stage IIB (n=2, 12.5%), stage III (n=1, 6.3%), and stage IV (n=4, 25%). The UICC stage distribution in the non-surveillance group (n=431) was stage 0 (n=4, 0.9%), stage IA (n=28, 6.5%), stage IB (n=27, 6.3%), stage IIA (n=86, 20.0%), stage IIB (n=48, 11.1%), stage III (n=56, 13.0%), and stage IV (n=182, 42.2%). The HCC surveillance group had significantly more patients with stage 0 disease than with stages IA through IV (P=.02). Similar results were observed when including stages IA (P=.007) and IB (P=.004) as early stages but not stage IIA (P=.10). A dilated pancreatic duct led to a PC diagnosis in all 6 patients with stage 0 disease.

Conclusion: Patients with HBV- and HCV-related chronic liver disease had an early PC diagnosis during HCC surveillance. Careful evaluation of the pancreas is warranted during HCC surveillance.

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The global number of patients with pancreatic cancer (PC) is increasing,[1] and PC is one of the most common cancers in Japan, where it is the fifth leading cause of cancer deaths among men and the third leading cause among women.[2] The prognosis of PC is dismal, with the worst 5-year survival rate of major malignancies (5%-10%), which is related to the lack of an algorithm that can facilitate a diagnosis at an early stage.[3] Although there are various known risk factors for PC, such as diabetes and obesity,[4] there are no simple surrogate markers for efficiently diagnosing PC at an early stage.[5]

Most patients with PC are symptomatic and are diagnosed at an advanced stage after the detection of a masslike lesion during imaging. Furthermore, PC has an invasive behavior,[6] which makes it difficult to diagnose at an early stage. Thus, more than one half of the patients with PC have distant metastasis at their diagnosis, and as few as 20% of patients with newly diagnosed PC are eligible for surgical resection,[7] which is the only potentially curative treatment. Therefore, it is ideal that the patients are diagnosed by Union for International Cancer Control (UICC) stage IIA (without lymph node and distant metastasis). However, a recent study indicated that imaging-based detection of a dilated pancreatic duct or cystic lesions (ie, indirect features suspicious of PC) without a masslike pancreatic lesion (a direct feature) can lead to a diagnosis of PC at an early stage.[8] Thus, an intensive diagnostic algorithm for early-stage PC is being applied for patients with indirect features that are incidentally detected during imaging.[9,10]

Patients with chronic liver disease caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) have an increased risk of developing hepatocellular carcinoma (HCC).[11] Thus, the guidelines strongly recommend that these patients routinely undergo abdominal imaging surveillance for HCC, regardless of whether they have symptoms.[12-14] Interestingly, some of these patients may have incidental extrahepatic imaging findings during the HCC surveillance. However, the association between HCC surveillance and early diagnosis of PC in patients with HBV- and HCV-related chronic liver disease is unknown. Therefore, the Ehime Pancreato-Cholangiology (EPOCH) Study Group designed this study to determine whether patients with HBV- and HCV-related chronic liver disease who were undergoing surveillance for HCC were diagnosed as having PC at an early stage.

PATIENTS AND METHODS

In this retrospective study, we examined data from 520 consecutive patients diagnosed as having PC from January 1, 2011, through December 31, 2013, at Ehime University Hospital and its affiliated centers (EPOCH Study Group). The diagnosis of PC was based on tumor markers, abdominal imaging, or histologic findings, as previously described.[7] The present study examined data regarding age, sex, likelihood of PC diagnosis, UICC stage (7th edition)[15] at PC diagnosis, and markers for viral hepatitis (hepatitis B surface antigen and antibodies to HCV). The staging of PC was generally based on the clinical stage, although the classification of stage 0 was determined pathologically. Based on the aim of the present study, patients without test results for viral hepatitis markers (n=73) were excluded.

The data are reported as mean ± SD or number and percentage. Intergroup comparisons were performed using the χ^2 test. Differences were considered statistically significant at 2-tailed $P<.05$. All the statistical analyses were performed using JMP software (version 13; SAS Institute Inc). Data were stored in a secure database, and patients were numerically coded to anonymize their data. The study's protocol complied with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of Ehime University Graduate School of Medicine.

RESULTS

Patient Characteristics

The cohort included 447 patients with PC (240 men and 207 women; mean ± SD age, 72±10 years; age range, 33-91 years). Forty-five patients (10%) were positive for either hepatitis B surface antigen (n=18, 4%) or anti-HCV (n=27, 6%), although none of them had coinfection. Of these 45 patients, 26 had newly diagnosed HBV/HCV infections at PC diagnosis; of the other 19 patients, 16 were undergoing periodic HCC surveillance, based on HBV- or HCV-related chronic liver disease, at their PC diagnosis (the HCC surveillance group) (Figure 1).

Distribution of the UICC Stages at PC Diagnosis

The overall distribution of the UICC stages at PC diagnosis was stage 0 (n=6, 1.3%), stage IA (n=31, 6.9%), stage IB (n=29, 6.5%), stage IIA (n=88, 19.7%), stage IIB (n=49, 11.0%),

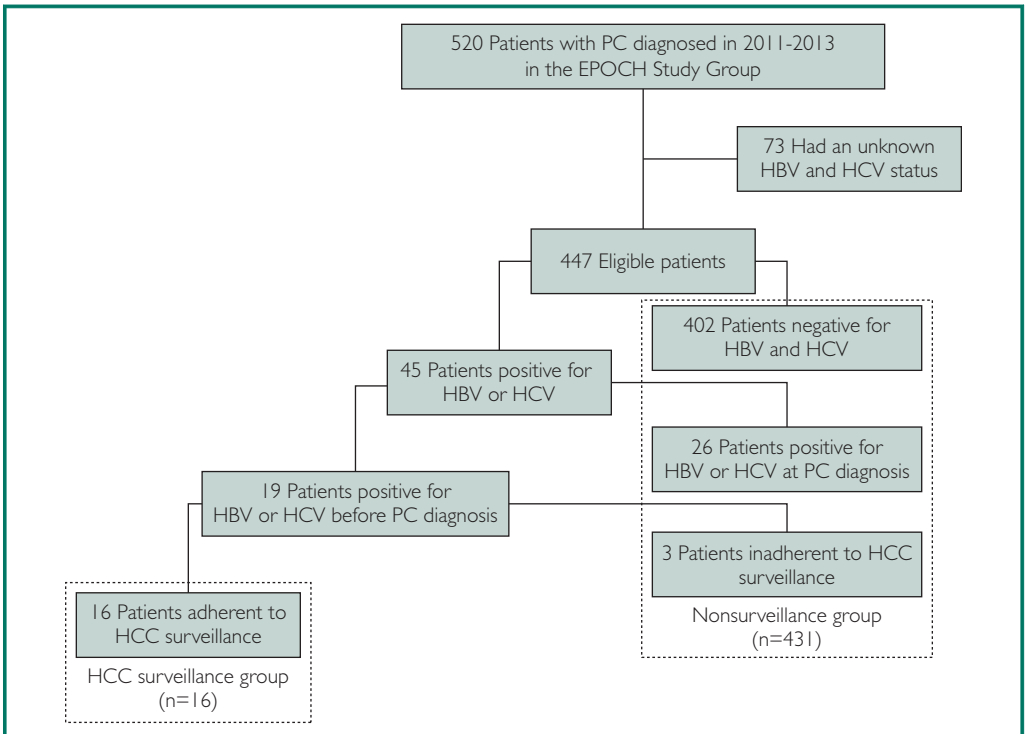

FIGURE 1. Study flow chart. Of 520 patients with pancreatic cancer (PC), 447 were included, and the hepatocellular carcinoma (HCC) surveillance group included 16 patients with PC who were undergoing HCC surveillance. EPOCH = Ehime Pancreato-Cholangiology; HBV = hepatitis B virus; HCV = hepatitis C virus.

stage III (n=58, 13.0%), and stage IV (n=186, 41.6%). In the HCC surveillance group (n=16), the distribution was stage 0 (n=2, 12.5%), stage IA (n=3, 18.8%), stage IB (n=2, 12.5%), stage IIA (n=2, 12.5%), stage IIB (n=2, 12.5%), stage III (n=1, 6.3%), and stage IV (n=4, 25%) (Figure 2). In the nonsurveillance group (n=431), the distribution was stage 0 (n=4, 0.9%), stage IA (n=28, 6.5%), stage IB (n=27, 6.3%), stage IIA (n=86, 20.0%), stage IIB (n=48, 11.1%), stage III (n=56, 13.0%), and stage IV (n=182, 42.2%) (Figure 2). A dilated pancreatic duct led to the diagnosis of PC in all 6 patients with pathology-proven stage 0 disease after resection.

Comparing UICC Stages Between the HCC Surveillance and Nonsurveillance Groups

When we compared the very early stage (stage 0) and the remaining stages (stages IA-IV), we found that the HCC surveillance group had significantly more patients with very-early-stage disease (12.5% vs 0.9%; P=.02). Similar results were observed when stages IA and IB were included as early stages (stages 0-IA vs stages IB-IV: P=.007; stages 0-IB vs stages IIA-IV: P=.004). However, no significant difference was observed when stage IIA was included as an early stage (stages 0-IIA vs stages IIB-IV; P=.10).

Sample Case

A male patient in his early 80s with HCV-related liver cirrhosis had a history of HCC. He was undergoing HCC surveillance every 3 months (combined ultrasonography, enhanced computed tomography [CT], and tumor markers), which provided no notable findings until enhanced abdominal CT revealed a dilated main pancreatic duct (diameter, 5 mm), which was associated with atrophy of the pancreatic body and tail (Figure 3A). Magnetic resonance cholangiopancreatography (Figure 3B) and endoscopic retrograde pancreatography (ERP)

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(Figure 3C) confirmed the dilated pancreatic duct. Further investigation, which included analysis of pancreatic juice that had been retrieved during the ERP, supported a suspicion of Papanicolaou class V cytology (Figure 3D). Thus, he underwent distal pancreatectomy (Figure 4A), and the final pathologic diagnosis was pancreatic intraepithelial neoplasia-3 (UICC stage 0) (Figure 4B) and pancreatic intraepithelial neoplasia-2 (Figure 4C).

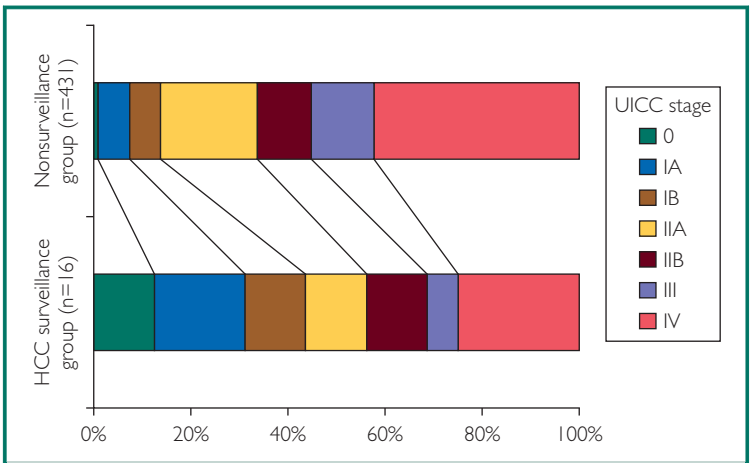

FIGURE 2. Distribution of the Union for International Cancer Control (UICC) stages at the diagnosis of pancreatic cancer. HCC = hepatocellular carcinoma.

DISCUSSION

The present study revealed 2 main findings. First, patients with HBV- and HCV-related chronic liver disease who were undergoing surveillance for HCC could be diagnosed as having PC at an early stage. Second, even patients who were undergoing HCC surveillance were frequently diagnosed at an advanced stage, with 25% of those patients having distant metastasis.

The first main finding is related to the fact that surveillance for HCC involves routine abdominal imaging, regardless of whether the patient has clear symptoms. Thus, it may be important to focus on both the liver and the pancreas during this imaging, with care taken to determine whether a dilated pancreatic duct or cystic lesions are present. Because 25% of the HCC surveillance group was diagnosed as having distant metastasis, even standard of care is carefully evaluating the pancreas on all abdominal imaging studies. Furthermore, although the EPOCH Study Group focuses on pancreatic and biliary diseases, some members are board-certified hepatologists who provide good knowledge of both PC and chronic liver disease. However, in the general clinical setting, it is important to improve our understanding of the indirect findings of PC because patients with suspected PC must be referred to specialists and undergo endoscopic ultrasonography and ERP, in addition to more general magnetic resonance cholangiopancreatography and contrast-enhanced CT.[16] Therefore, radiologists, ultrasonographers, and nonspecialists should be educated regarding the indirect findings of PC because any form of imaging follow-up (eg, postoperative screening for malignant disease) may help facilitate the early diagnosis of PC. Thus, the diagnosis of PC tumors with a diameter less than 10 mm could help improve 5-year survival to greater than 80%.[17]

There are several possible explanations for the second main finding. First, the pancreas, and especially the pancreatic tail, can occasionally be difficult to visualize during ultrasonography. Second, pancreatic duct dilation is limited to a short range when the neoplastic lesion exists in the pancreatic tail, despite the tail being visualized. It may be possible to address these issues using contrast-enhanced CT if the incidence of PC is as high as the annual incidence of HCC, which is approximately 5% in patients with HBV- and HCV-related chronic liver diseases.[18] However, this strategy seems impractical given that these patients do not have a high risk of PC and the prevalence of PC is low.[19] Therefore, patients with HBV- and HCV-related chronic liver diseases should be managed according to the HCC surveillance guidelines.

The present study has several limitations. The first is the retrospective design, as we did not have access to data regarding the tumor location or exact timing of the last abdominal imaging. Second, the prevalence of HBV and HCV infection in the present

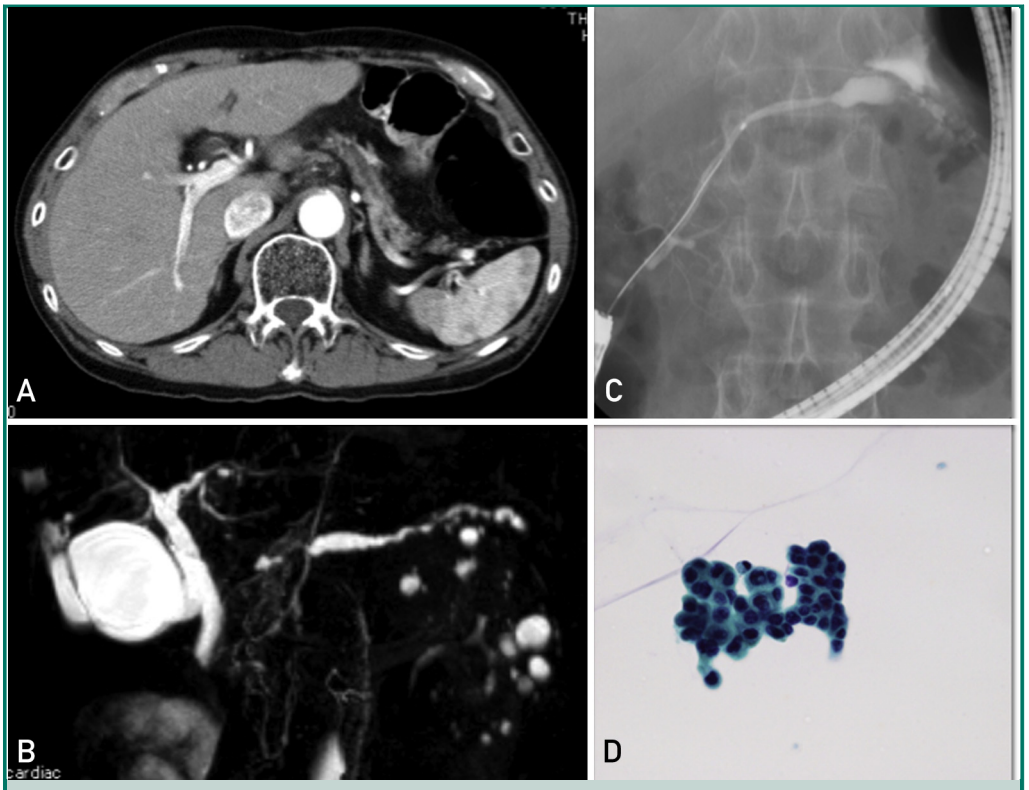

FIGURE 3. Preoperative imaging findings from a patient with pancreatic cancer. The arterial phase of contrast-enhanced abdominal computed tomography revealed a dilated main pancreatic duct, which was associated with atrophy of the pancreatic body and tail (A). Magnetic resonance cholangiopancreatography revealed a stricture in the main pancreatic duct, with dilation of the peripheral duct (B). Similar findings regarding the main pancreatic duct were observed during endoscopic retrograde pancreatography, and pancreatic juice was collected (C), which supported a suspicion of Papanicolaou class V cytology (D).

study (10%) was higher than that in the general Japanese population (HBV: 0.9% and HCV: 1.64% among 70- to 74-year-old Japanese individuals).[20] Third, we did not have final staging data for all the patients because the intraoperatively estimated surgical stage was used for patients who could not complete surgical resection because of liver metastasis or dissemination, and the pathologic stage was used for patients who completed surgical resection. However, many physicians select the initial management strategy based on the clinical stage. Fourth, one might argue about the small number of patients in the HCC surveillance group (n=16), especially those who were diagnosed at stage 0 (n=2). Nevertheless, it is worthwhile to note that even when early stage was expanded up to stage IB, which is still within the resectable stage without metastasis, the HCC surveillance group had significantly more patients with PC at an early stage. Fifth, we focused on the stage at diagnosis of PC in this study, thus, the long-term outcome of these patients is unclear. Finally, although this was not an observational study of continuous patients with HBV- and HCV-related chronic liver disease undergoing HCC surveillance, false-positive findings of pancreatic lesions during HCC surveillance may lead to unnecessary procedures being performed. However, to our knowledge, there is no study showing the impact of incidentally detected pancreatic lesions during HCC surveillance. Furthermore, patients with HBV- and HCV-related chronic liver disease do not have a high risk of PC, and the prevalence of PC

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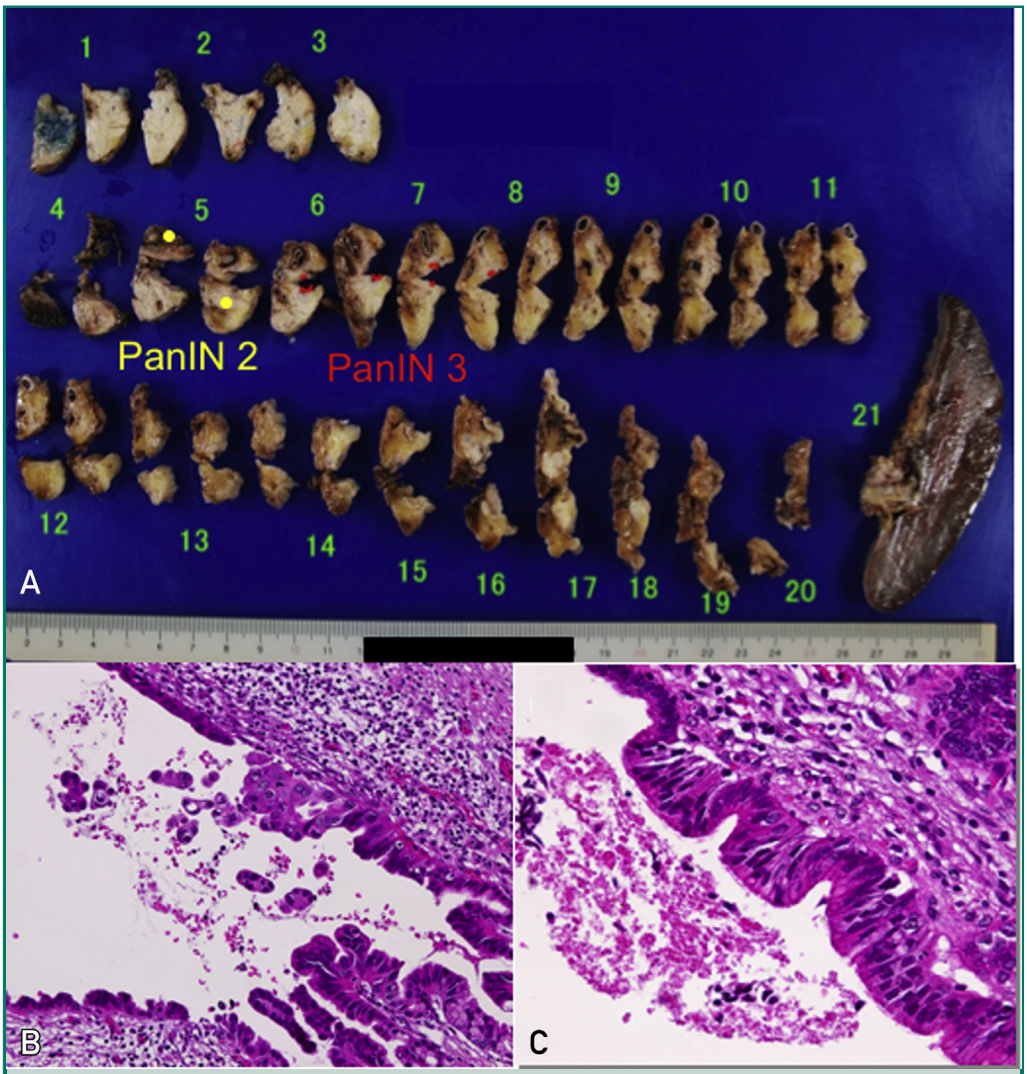

FIGURE 4. Postoperative pathologic findings from a patient with pancreatic cancer. Mapping of the resected surgical specimen (A) revealed pancreatic intraepithelial neoplasia-3 (PanIN3) (hematoxylin-eosin, original magnification × 100) (B) along the main pancreatic duct (red dots) and PanIN2 (hematoxylin-eosin, original magnification × 400) (C) in the parenchyma of the pancreas (yellow dots). The pathologic features of PanIN3 were high-grade atypia and papillary proliferation in the epithelium of the main pancreatic duct, loss of nuclear polarity, abnormal mitoses, and nuclear irregularities (B).

is low. Despite these limitations, it is important to identify efficient surrogate markers for PC, which can facilitate its early diagnosis and treatment. Thus, the present findings may be useful in this context, especially when screening populations with elevated prevalence of HBV and HCV infection and patients with nonalcoholic fatty liver disease or a history of colorectal cancer because they share risk factors with PC (eg, diabetes and obesity).

CONCLUSION

Patients with HBV- and HCV-related chronic liver disease who underwent surveillance for HCC were diagnosed as having PC at a relatively early stage. Therefore, careful observation of the pancreas and special attention to the indirect features of PC are important during HCC surveillance. However, it is unclear whether patients who are diagnosed as having early-stage PC during HCC surveillance experience improved long-term outcomes because

they may have advanced liver disease, which could alter the approach to managing PC. Nevertheless, the present findings indicate that even retrospective review of imaging findings may be useful for identifying features of PC (eg, a dilated pancreatic duct or cystic lesions), which could facilitate the diagnosis of early-stage PC before a masslike lesion can be detected. Further studies are needed to address these issues.

Abbreviations and Acronyms: **CT** = computed tomography; **ERP** = endoscopic retrograde pancreatography; **HBV** = hepatitis B virus; **HCC** = hepatocellular carcinoma; **HCV** = hepatitis C virus; **PanIN** = pancreatic intraepithelial neoplasia; **PC** = pancreatic cancer; **UICC** = Union for International Cancer Control

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