Longterm Follow-up of Small Pancreatic Cystic Lesions in Liver Transplant Recipients

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Incidental small pancreatic cystic lesions (PCLs) are often found on preoperative imaging in patients undergoing orthotopic liver transplantation (OLT). Although these are considered benign or of low malignant potential, the influence of immunosuppression after OLT may be of concern. The aim of this study was to observe the longterm outcome of these small PCLs in post-OLT patients. An institutional OLT database of 1778 consecutive OLT patients from January 2000 to December 2010 was analyzed. Computed tomography, magnetic resonance imaging, or endoscopic ultrasound at the time of OLT and all subsequent imaging, cytology, fluid analysis of PCLs, and patient status were evaluated. A total of 70 patients with 182 PCLs, of benign or low malignant potential, were identified with a mean follow-up time of 64 months. At initial diagnosis of PCLs in 48 patients, 7 branch duct–type intraductal papillary mucinous neoplasms (B-IPMNs), 1 serous cystadenoma (SCA), and 40 nonspecific benign cysts were identified. Final diagnosis at the end of the follow-up revealed 16 B-IPMNs, 3 SCAs, and a mixed acinar-neuroendocrine carcinoma, in which the latter developed 9 years after initial diagnosis of B-IPMN. During the follow-up time, average increase in size and number of PCLs were 4.5 mm and 1.4, respectively ($P < 0.001$ for both). The majority of incidental PCLs in OLT patients showed an indolent behavior despite immunosuppression. Risk of malignancy development was very low and comparable with normal population.

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Orthotopic liver transplantation (OLT) has become a very successful procedure in the treatment of end-stage liver disease and other liver diseases. Advances in immunosuppressive agents have improved the survival rates of organ transplant grafts.[1] The evaluation of the patient before OLT is critical to assure a favorable outcome. During this evaluation, unexpected underlying conditions may be discovered that will need to be addressed before the liver transplantation (LT) or may even contraindicate the LT itself. Cross-sectional imaging for preoperative workup and follow-up are routinely done in patients being considered for OLT. As a result, many incidental pancreatic cystic lesions (PCLs) may be found in these patients. The incidence of detected PCLs has increased in recent years as imaging methods improved in spatial and contrast resolution. Studies have shown incidence of PCLs in 0.7%-44.7% in the general population,[2-7] whereas it may be as high as 58.8%-59.6% in LT recipients, using magnetic resonance cholangiopancreatography (MRCP).[7,8] Many of these cystic lesions are small and indeterminate in nature at the time of first discovery. Their spectrum includes benign, premalignant, and malignant pathologies. Serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), and

Abbreviations: B-IPMN, branch duct–type intraductal papillary mucinous neoplasm; CEA, carcinoembryonic antigen; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; HBV, hepatitis B virus; HCV, hepatitis C virus; IPMN, intraductal papillary mucinous neoplasm; LT, liver transplantation; MANEC, mixed acinar-neuroendocrine carcinoma; MCA, mucinous cystadenoma; MCN, mucinous cystic neoplasm; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis; OLT, orthotopic liver transplantation; PCL, pancreatic cystic lesion; SCA, serous cystadenoma; SCN, serous cystic neoplasm; SD, standard deviation.

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intraductal papillary mucinous neoplasm (IPMNs) are the most common types. SCNs have a benign behavior and require no treatment. MCNs and IPMNs are considered neoplasms with malignant potential. IPMNs that involve the main pancreatic duct (MPD; main or mixed duct IPMNs) have a higher malignant potential, and surgical resection is recommended for these lesions. In contrast, branch duct–type intraductal papillary mucinous neoplasms (B-IPMNs) are associated with a lower risk of malignant transformation. The risk of malignant progression is a concern, especially in a patient who will need lifelong immunosuppression. One study in solid organ transplant recipients showed that the development of cancer is rare in PCLs without high-risk features.[9] There are limited data regarding the behavior of PCLs and risk of progression of B-IMPNs in patients undergoing LT. One study in solid organ transplant recipients showed that in PCLs without high-risk features, the development of features worrisome for cancer is rare.[9] Another study followed LT recipients with B-IPMNs and did not find a significant difference in the risk of developing high-risk features between the LT and control groups.[10] The aim of this study is to observe the clinical behavior of PCLs in patients undergoing LT on chronic immunosuppression.

Patients and Methods

The study was performed with Health Insurance Portability and Accountability Act compliance and institutional review board approval. From the institutional LT database between January 2000 to December 2010, 1778 consecutive adult OLT patients were identified, and their electronic records were searched for all magnetic resonance imaging (MRI) and computed tomography (CT) imaging reports for presence of PCLs. Image reviews were performed on a PACS-integrated workstation (Centricity RA 1000, GE Healthcare, Little Chalfont, UK) with a 21.5-inch display and a resolution of 1920×1080 pixels. Patients were excluded if they had clinical pancreatitis, history of prior pancreatic surgery, congenital syndromes such as autosomal-dominant polycystic kidney disease, autosomal-dominant polycystic liver disease, Von Hippel–Lindau syndrome, cystic fibrosis, and high-potential malignant pancreatic cystic neoplasms based on initial characteristic CT/MRI and endoscopic ultrasound (EUS) findings. Minimum follow-up time was 6 months. Demographic data of the patients, including age, sex, causes of cirrhosis and OLT, EUS studies, cytological report, fluid analysis, patient status, and comorbidities were retrospectively reviewed.

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IMAGING ANALYSIS

The most suitable images of sufficient quality from CT and MRIs were chosen for analysis and measurement. CT must be contrast-enhanced with slice thickness $\leq$5 mm. MRI and MRCP have either contrast-enhanced T_1-weighted images and/or T_2-weighted images of sufficient resolution and free from motion artifact. We excluded questionable PCLs of <3 mm in size that could not be confirmed by at least 2 studies. Sizes of PCLs were measured by the longest axial diameter of the largest PCL in each patient. Growth rate of the dominant PCL at presentation was determined and calculated by a difference of the maximum axial diameter of the lesion over time divided by follow-up time period (mm/year). Number of PCLs in each patient was counted up to 10 and regarded as the maximum number per patient.

CLASSIFICATION OF PCLS

PCL classification was based on imaging features and fluid analysis if available. Each PCL was classified by consensus agreement between 2 abdominal radiologists (D.S.L. and S.V. with 20 and 3 years of experience, respectively). Size measurements for growth were made by 1 radiologist (S.V.).

An imaging diagnosis of a nonspecific pancreatic cyst was defined as a cyst of <3 cm with a round or oval shape, sharp demarcation, thin walls, no more than 1 thin septum, and homogeneous fluid signal, density, or simple fluid echogenicity. Additional endoscopic criteria included cyst fluid aspiration and analysis negative for mucin stain, mucin-producing cells, malignant cells, and low carcinoembryonic antigen (CEA) level (<5 ng/mL). Imaging diagnosis of a presumed serous cystadenoma (SCA) would be made if the lesion was comprised of a cluster of numerous small cysts with or without a central scar, which could be calcified or noncalcified.[11,12] Further confirmation of SCA could be made on fluid analysis yielding serous fluid and/or

TABLE 1. Demographic Characteristics of the Patients

Characteristic	Value (n = 70)
Age, years	58 ± 9.4 (29-74)
Sex	
Male	39 (55.7)
Female	31 (44.3)
Cause of cirrhosis	
HBV	8 (11.4)
HCV	37 (52.9)
Alcohol	8 (11.4)
NASH	1 (1.4)
Others*	16 (22.9)
PCLs follow-up time in months	64 ± 39 (6-147)
Post-OLT follow-up time in months	55 ± 39 (6-161)

NOTE: Data are given as n (%) or mean ± SD (range).
*Others are including primary sclerosing cholangitis, primary biliary cirrhosis, fulminant hepatitis, etc.

cytology staining positive for cystoplasmic glycogen, low CEA level (<5 ng/mL), and low amylase level (≤100 units/L).[13,14]

Presumed diagnosis of a mucinous lesion of low malignant potential, ie, mucinous cystadenoma (MCA) or B-IPMN, were based on imaging and available cyst fluid analysis demonstrating positive mucin stain or CEA > 192 ng/mL, or presence of mucin-producing cells.[13-15] Lesions were classified as MCA when a unilocular cyst up to 3 cm with or without mild septation, mural thickening, or enhancement was seen without communication with the pancreatic duct.[16] Lesions were classified as B-IPMN when either unilocular or multilocular PCLs <3 cm were present with at least 1 cyst communicating with a nondilated MPD, or more than 4 PCLs < 3 cm were present but none clearly communicating with a nondilated MPD. If the imaging diagnosis of PCLs was different from that based on fluid analysis and cytology, the latter would determine the final diagnosis.

STATISTICAL ANALYSIS

The results from statistical analysis were reported in mean, range, and standard deviation (SD). Paired *t* test was used to compare the value of means from baseline and follow-up imaging size. A *P* value < 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS version 20.0 for windows (IBM, Armonk, NY).

Results

A total of 70 OLT patients (70/1778, 4%) had 182 PCLs. There were 39 (39/70, 55.7%) males and 31 (31/70, 44.3%) females. Patients' age ranged from 29 to 74 years, with a mean ± SD of 58 ± 9.4 years. Patient demographics and etiologies of cirrhosis were listed in Table 1. All PCLs at baseline imaging were less than 3 cm. In 58 (58/70, 83%) patients, PCLs were found during preoperative workup and in 12 (12/70, 17%) patients PCLs were first seen after OLT. Twelve patients underwent EUS before OLT for confirmation, and 8 patients received EUS after OLT (Table 2). All EUS were done with cyst fluid aspiration except in 2 patients (1 with coagulopathy and the other with unknown reason). The mean cyst follow-up time was 64 ± 39 (range, 6-147) months with 16% (11/70) of the patients exceeding 108 months (9 years) of follow-up.

TABLE 2. Finding of 20 EUS Patients (18 with FNA)

Diagnosis	Pre-OLT (n = 12)	Post-OLT (n = 8)
Nonspecific pancreatic cyst	4	2
Pseudocyst	1	3
SCA	2	0
MCA	0	0
B-IPMN	5	2
Other	0	1 (MANEC)

A majority of PCLs at baseline radiological imaging evaluation were benign-appearing pancreatic cysts of at most low malignant potential. Most of the cysts were small with mean initial size ± SD of 8 ± 4.9 mm and solitary (52/70; 74%). Septated cysts were present in 5 (5/70, 7%) patients. No PCLs demonstrated any mural nodules or calcifications at the time of initial imaging diagnosis. Imaging evaluation before OLT showed 7 (7/70, 10%) B-IPMNs, 1 (1/70, 1.4%) SCA, and 40 (40/70, 57%) nonspecific benign cysts. During the follow-up period, PCLs disappeared in 4 (4/70, 6%) patients, decreased size in 7 (7/70, 10%) patients, the size stayed stable in 21 (21/70, 30%) patients, and increased size in 38 (38/70, 54%) patients. There were 28 (28/70, 40%) patients who had an increase in the number of PCLs. A comparison between initial imaging and the last available imaging in patients with PCLs showed statistically significant ($P < 0.001$) increase in size (from 6.0 ± 5.9 to 10.5 ± 6.6 mm) and number (from 1.2 ± 0.9 to 2.6 ± 2.6), an example of increasing size of the cyst shown in Fig. 1. The average growth rate of PCLs was 0.5 ± 1.2 (95% CI, –2.0-5.5) mm/year.

Morphologic changes of PCLs were observed in 7 (7/70, 10%) patients, including newly developed septations in 4 (4/70, 5.7%) patients, cluster appearance in 1 (1/70, 1.4%) patient, and progression into diffused pancreatic involvement by PCLs in 2 (2/70, 2.8%) patients, 1 of whom also had new cyst septations and mural calcifications. Only a single patient ultimately

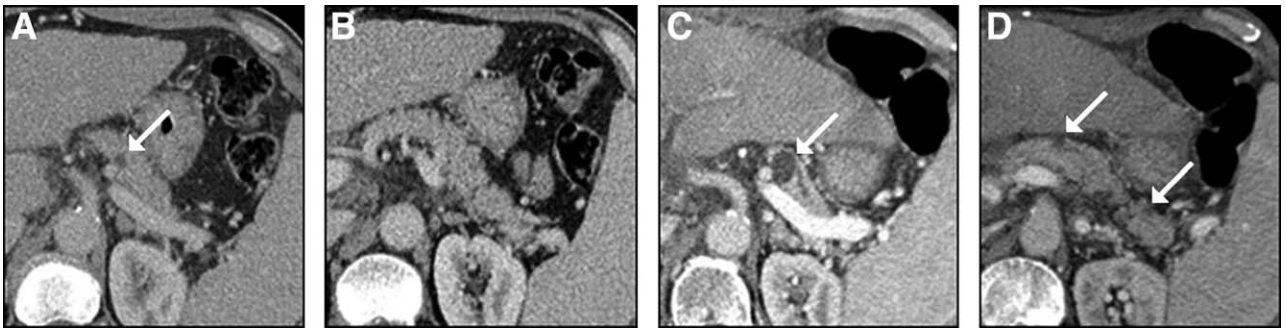

FIG. 1. A 55-year-old male patient who received OLT due to HCV cirrhosis. Pre- and post-LT CT show increasing size and number of PCLs. (A) Pre-LT, venous phase axial CT image shows a small pancreatic cyst at the head of the pancreas (arrow). (B) Pre-LT, venous phase axial CT image shows absence of additional cysts in the rest of the pancreas. (C) At 4 years after LT, venous phase axial CT image shows interval increase in size of the cyst in the pancreatic head from 0.5 to 1.2 cm (arrow). (D) At 4 years after LT, a venous phase axial CT image shows 2 new small pancreatic cysts in the body and tail of the pancreas (2 arrows).

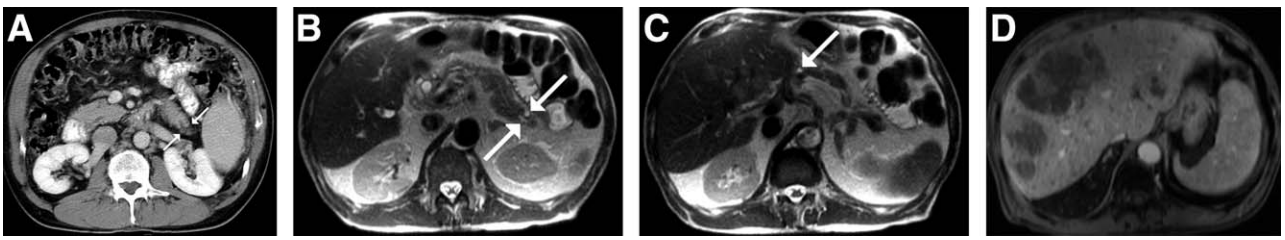

FIG. 2. A 60-year-old male patient who received OLT due to HCV cirrhosis and HCC. Nine years after OLT, this patient presented with multiple liver metastasis from MANEC. (A) Pre-LT, venous phase axial CT image shows tiny small pancreatic cysts in the tail of the pancreas (arrows). (B) Axial T_2-weighted MRI 9 years after LT shows stability of the cysts in the pancreatic tail (arrows). (C) T_2-weighted MRI 9 years after LT showing a newly developed 0.6 cm cyst at genu of the pancreas (arrow). Biopsy revealed diagnosis of MANEC. (D) T_1-weighted MRI post-gadolinium at the portovenous phase shows multiple liver metastasis. Biopsy revealed neuroendocrine tumor liver metastasis.

TABLE 3. Final Diagnosis and Progression of Cysts in All Patients at the End of Follow-up

		Size Changes During Follow-up		
Diagnosis	Patients, n (%)	Increase	Stable	Decrease
Nonspecific pancreatic cyst	46 (65.7)	24	17	5
Pseudocyst	4 (5.7)	3	0	1
SCA	3 (4.3)	2	0	1
B-IPMN	16 (22.9)	14	0	2*
MANEC	1 (1.4)	0	0	1*

*The size of cysts decreased after EUS and FNA.

had a proven malignant pancreatic cyst (Fig. 2). This patient had 2 small simple 7-mm and 12-mm PCLs in the pancreatic tail at the time of OLT. No initial EUS was performed. After 9 years (115 months) post-OLT follow-up, patient presented with metastatic liver disease and biopsy showed mixed acinar-neuroendocrine carcinoma (MANEC). At this time, the pancreas showed stable size of the 2 initial cystic lesions (7 and 12 mm) at the tail of the pancreas, but there was a small additional cyst found in the neck (6 mm). Subsequent EUS with fine-needle aspiration (FNA), cytology, and immunohistochemistry showed that this new cyst was in fact also MANEC. The patient died 1 year after he was diagnosed. Among patients with either imaging or fluid analysis–based diagnosis of B-IPMN, or SCA at baseline, none of the patients developed proven malignancy during the follow-up period. Final diagnosis and progression of cysts after longterm follow-up are shown in Table 3.

Discussion

Results from our study showed a PCL prevalence of 4% (70/1778) in our OLT patient cohort. This rate was comparable to that of the general population (0.7%-44.7%).[2-7] Not surprisingly, this prevalence was notably lower than previous studies in LT patients using 3-dimensional T_2-weighted MRCP (58.8%-59.5%)[8] because our detection was based on predominantly standard contrast-enhanced CT and MR sequences without MRCP. Our study showed only 1 patient (1/70, 1.4%) who developed malignancy during the follow-up time of 64 months. This was consistent with prior population studies examining the malignancy rate of PCLs, with 1 study showing a rate of 0.8% (14/1735 patients) and another 3.6% (4/112 patients) with a follow-up period of 23.4 months (mean) and 72.3 months (median).[10,17] Likewise, the low rate of malignant transformation of B-IPMN was also in keeping with that reported in the general population[18-22] and solid organ transplant recipients.[9,10,23,24] These findings were also similar to that of Gill et al. whose study of B-IPMN showed no difference in malignant transformation rate between the normal population and solid organ transplant recipients.[22] Our study, however, provided additional evidence with much longer-term follow-up (64 versus 29 months).

For the general population, many professional societies have proposed guidelines for the management[10,14,23,25] of incidental PCLs.[14,18,23,25-28] The same general guidelines that have been used at our institution appeared to have succeeded in yielding a low-risk population, which did not have an increased malignant transformation rate compared with the general population despite OLT and immunosuppression. The fact that there was only 1 case of malignancy in our cohort that appeared only after 9 years after OLT also argues against immunosuppression being a contributing factor (Fig. 2). Therefore, similar to the general population, most small cysts are benign in behavior, including B-IPMNs. Presence of these lesions should not preclude OLT candidacy. While awaiting transplantation, the lesions are already closely monitored, and after transplantation routine monitoring is adequate because there is no increase risk for malignancy despite immunosuppression.

Limitations of our study included the single institution retrospective nature of the study, lack of standardized imaging modality or frequency, and lack of pathological diagnosis for all cysts. The strengths of our study, however, were the relatively large OLT cohort and long follow-up time.

In conclusion, small incidental PCLs with low malignant potential, including B-IPMNs, displayed an indolent behavior in our cohort of OLT patients despite longterm immunosuppression.

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