Original Article

Pancreatic adenocarcinoma in liver transplant recipients: a case series

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Background: Malignancy is one of the known leading causes of death among long-term liver transplantation (LT) survivors. Pancreatic cancer has an incidence of 7.6/100,000 in North America and constitutes a diagnostic challenge post-LT.

Methods: This is a single-center, retrospective review of the electronic health records (EHRs) of LT recipients with pancreatic adenocarcinoma (1990–2019). The prevalence of pancreatic adenocarcinoma in our institutional non-LT population was assessed using an institutional de-identified database (Synthetic Derivative).

Results: Six out of 2,232 (0.27%) LT recipients were diagnosed with pancreatic adenocarcinoma. Median age at diagnosis was 66.0 years (IQR, 57.8–71.8 years). Median time from LT to pancreatic adenocarcinoma diagnosis was 8.9 years (IQR, 4.7–16.2 years), the median size on imaging was 3.2 cm (IQR, 3.1–4.7 cm), and all tumors were located on the head of the pancreas. Three patients underwent surgical resection (one with adjuvant chemotherapy), two underwent palliative care, and one palliative chemotherapy with gemcitabine and abraxane. Over a median follow-up of 220.5 days (IQR, 144.8–399.5 days), all six patients died due to disease progression (100%). Pancreatic adenocarcinoma was diagnosed in 5,033 out of 2,484,772 (0.20%) individuals in the Synthetic Derivative.

Conclusions: Our findings identified an increased incidence of pancreatic adenocarcinoma following LT compared to the general population.

Keywords: Liver transplantation (LT); pancreatic adenocarcinoma; malignancy; immunosuppression; case series

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Introduction

From the time of the first liver transplantation (LT) reported by Starzl *et al.* in 1963 and the emergence of transplantation as a field of medicine in the 1980s, significant improvement in outcomes has been witnessed over the course of the last four decades (1). The median survival time has increased nearly fourfold for deceased donor LT recipients, and one-year survival has increased from around 30% to 92% (2-4). The long-term survival, however, has not significantly improved during the last two decades (4). Most of the long-term post-LT mortality is attributed to chronic immunosuppression, and malignancy is one of the leading cause of death among these patients, accounting for 16.4% of deaths (4). Post-LT malignancy in 1-year LT survivors was found to be the cause of death in 15% between 1987 and 1990 compared to 27% between 2011 and 2016 (4). A rising trend of *de novo* malignancies in long-term survivors has also been documented, and they account for approximately 30% of all 10-year post-LT mortalities (5). The incidence of *de novo* malignancies among transplant patients is two to fourfold higher than their healthy counterparts (6). These neoplasms exhibit aggressive behavior, appear at a younger age and have higher mortality in LT recipients (7). With solid organ malignancies, skin malignancies, and post-transplant lymphoproliferative disorders being at the top of the list, head and neck cancers, Kaposi sarcoma, lung, gynecological, genitourinary, colorectal, and gastrointestinal cancers have all been reported (6,8,9).

The high mortality rate of pancreatic cancer is well known. With 458,918 new cases and 432,242 deaths globally in 2018, pancreatic cancer was the 12th most common cancer and the 7th leading cause of cancer-related death worldwide with an incidence of 7.6 per 100,000 population in North America (10,11) and 7.7 per 100,000 population in Europe (11). It is more common in men (5.5 per 100,000) compared to women (4.0 per 100,00) (11), while the incidence for both sexes increases with age (10,11). Although the underlying reason for this disparity is unclear, it can be speculated that either women are less likely to be exposed to risk factors for pancreatic cancer or may be less susceptible to this type of cancer (11-13). Alcohol, smoking, obesity, and hepatitis C virus infection are significant risk factors for pancreatic cancer (5,14-17). As alcohol, obesity and hepatitis C virus infection are common causes of cirrhosis, pancreatic cancer is an important malignancy to be aware of post-LT.

Most of the data in the literature about LT and pancreatic cancer are focused on pancreatic neuroendocrine tumor. We sought to specifically describe the incidence and impact of post-LT pancreatic adenocarcinoma compared to pancreatic adenocarcinoma in our general population. We present the following article in accordance with the AME Case Series reporting checklist (available at https://dx.doi.org/10.21037/apc-21-4).

Methods

Institutional data

The Vanderbilt University Medical Center (VUMC) electronic health record (EHR) system was established in 1990 and includes data on billing codes from the International Classification of Diseases, 9th and 10th editions (ICD-9 and ICD-10), Current Procedural Terminology (CPT) codes, laboratory values, reports, and clinical documentation. The de-identified mirror of the EHR, known as the Synthetic Derivative, includes patient records on more than 2.8 million individuals.

Pancreatic adenocarcinoma cases were identified by the presence of any pancreatic adenocarcinoma ICD code (ICD-9: 157.X or ICD-10: C.25.X) in their EHR. Liver transplant cases were identified by the presence of the LT CPT code: 47135.

The prevalence of pancreatic adenocarcinoma was determined separately within the entire Synthetic Derivative sample and excluding individuals who received an LT. Next, the incidence of pancreatic adenocarcinoma after LT was determined by finding the number of individuals whose first pancreatic adenocarcinoma code occurred after their LT code.

Case series

The study included all adult (age 18 and above) LT recipients transplanted at VUMC from January 1, 1990, to December 31, 2019, who were diagnosed with pancreatic adenocarcinoma. A retrospective review of the VUMC EHR of LT recipients to identify patients with a diagnosis of pancreatic adenocarcinoma after LT was performed through text-search using the terms “pancreas”, “pancreatic”, “malignancy”, “malignant”, “tumor”, “cancer”, and “carcinoma”. We collected demographic, clinical, laboratory, and radiological data utilizing the EMR database and VUMC radiology database. The final diagnosis of pancreatic adenocarcinoma and inclusion of patients in

Table 1 Patient characteristics, management, and outcomes

Patient No. [year of LT]	LT diagnosis	Age (years)/sex	BMI (kg/m^2)	Smoking history	Alcohol abuse history	DM	Year of diagnosis	Tumor size on imaging (cm)	Management	Last disease extent	Status	Survival after diagnosis (days)
1 [1998]	HBV, hereditary hemochromatosis	71/M	21.8	No	No	Yes	2014	3.2	Resection + chemotherapy	M1 intraoperatively	Dead	360
2 [2000]	Alcoholic liver disease	74/F	25.3	Yes	Yes	No	2018	4	Palliative care	M1	Dead	154
3 [2010]	HCV, HCC (explant)*	66/M	20.2	Yes	Yes	Yes	2019	3	Palliative care	SMA invasion	Dead	260
4 [2010]	HCV, Alcoholic liver disease	48/M	22.1	Yes	Yes	No	2013	3.1	Resection	R1 resection, leading to M1	Dead	117
5 [2011]	HCV, iCCA (explant)*	66/F	27.3	Yes	Yes	No	2019	5.3	Palliative chemotherapy	SMA, SMV and celiac axis invasion	Dead	181
6 [2013]	NASH, HCC	61/M	25.8	Yes	No	Yes	2018	NA	Resection → palliative care	Disease-free → M1	Dead	518

*, HCC and iCCA were identified on explant pathology and not pre-operatively. BMI, body mass index; DM, diabetes mellitus; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; LT, liver transplantation; M, male; M1, metastatic disease; MMF, mycophenolate mofetil; NA, not available; NASH, nonalcoholic steatohepatitis; R1, positive-margin resection; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

our study was determined after a review of biopsy/surgical specimen pathology reports. All data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at VUMC (18,19); REDCap is a secure, web-based software platform designed to support data capture for research studies. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Vanderbilt University Medical Center Institutional Board Review (IRB#192061) and individual consent for this retrospective analysis was waived.

Statistical analysis

Continuous variables were summarized as medians and interquartile ranges (IQR), and categorical variables were summarized as frequencies and percentages. Statistical analysis was performed using IBM SPSS Statistics 26 software (IBM Corp., Armonk, NY, USA).

Results

Institutional data

The VUMC Synthetic Derivative contained ICD information on 2,484,772 individuals, including 5,033 individuals who had pancreatic adenocarcinoma and 1,711 who received an LT. Among LT recipients, eight also had a pancreatic adenocarcinoma code (two had their first pancreatic adenocarcinoma code prior to LT, and six had their first pancreatic adenocarcinoma code after LT). The prevalence of pancreatic adenocarcinoma in the entire Synthetic Derivative was 0.20%. Within individuals who did not receive an LT, the prevalence of pancreatic adenocarcinoma was 0.20%. The incidence of pancreatic adenocarcinoma after LT was 0.35%.

Case series

Six patients who developed pancreatic adenocarcinoma after LT were identified. Based on Organ Procurement and Transplantation Network data, 2,232 LTs in adults were performed in our institution between 1990 and 2019, leading to an incidence of 0.27%. Detailed patient characteristics and outcomes are presented in *Table 1*. The median age at the time of pancreatic adenocarcinoma diagnosis was 66.0 years (IQR, 57.8–71.8 years). Four patients were male (66.7%), the median body mass index

Table 2 Clinical manifestations

Manifestation	n (%)
Elevated bilirubin	5 (83.3)
Jaundice	4 (67.7)
Abdominal pain	3 (50.0)
Weight loss	3 (50.0)
Weakness	2 (33.3)
Elevated glucose	1 (16.7)
Pancreatitis	1 (16.7)
Depression	0 (0.0)

was 23.7 (IQR, 21.4–26.2), 5 had a history of smoking (83.3%), and 4 had a history of alcohol abuse (66.7%). All patients remained abstinent of alcohol use post-LT and patients received standard immunosuppression with a calcineurin inhibitor, steroids and mycophenolate mofetil. The patients' clinical manifestations are presented in *Table 2*. The median time from LT to pancreatic adenocarcinoma diagnosis was 8.9 years (IQR, 4.7–16.2 years), the median size on imaging was 3.2 cm (IQR, 3.1–4.7 cm), and all tumors were located on the head of the pancreas. The initial diagnosis was established via computed tomography (CT) scan in all but one patient. This one patient was found to have endoscopic findings consistent with malignancy, but the CT scan failed to identify any pancreatic lesions. Carbohydrate antigen 19-9 level was requested in three patients and was found to be elevated (mean, 110 U/L; range, 40–236 U/L). Three patients underwent surgical resection (one with adjuvant FOLFOX chemotherapy), two underwent palliative care, and one palliative chemotherapy with gemcitabine and abraxane. Over a median follow-up of 220.5 days (IQR, 144.8–399.5 days), all six patients died due to disease progression (100%).

Discussion

Our single institution series shows that the incidence of pancreatic adenocarcinoma after an LT is comparable to that of our hospital population (0.27–0.35% *vs.* 0.20%), yet it is higher than that reported in the general population of North America (0.0076%) (10,11). The incidence of pancreatic adenocarcinoma in our hospital population is different from that of the general population, as our center is a large tertiary care referral center and therefore, many patients are referred for advanced care of complex disease processes, and they represent a subgroup with a higher incidence of comorbidities.

Improved outcomes following LT has led to patients living longer following LT. This increased longevity has highlighted the significance of *de novo* malignancies. The incidence of *de novo* malignancies among LT recipients is 2–4 times higher than in the general population (20,21). A recent systematic review showed that post-transplant lymphoproliferative diseases and skin tumors are the most commonly seen malignancies after LT (6). The incidence of *de novo* solid-organ malignancy following LT ranges from 3–15% (22). Reported risk factors for the development of *de novo* malignancy include increasing age, male sex, white race, and prior malignancy (23). Importantly, survival with *de novo* malignancy in LT patients is worse when compared to the general population and to the population of cancer-free LT recipients (24).

There are no large studies in the literature reporting incidence or outcomes of LT recipients with pancreatic malignancies except for single case reports or small case series, also suggesting that pancreatic adenocarcinoma is not among the most common post-LT malignancies. When examining the SRTR database from 1987–2015, Bhat *et al.* found that *de novo* pancreatic cancer was reported in only 0.18% of the LT population. These patients were grouped with other rare malignancies as "Other" and not analyzed (23). Most pancreatic tumors reported in the literature are neuroendocrine type while only a handful of cases of adenocarcinoma are reported (5,25-29) (*Table 3*).

Post-LT pancreatic adenocarcinoma poses a significant diagnostic challenge, as symptoms of obstructive jaundice are usually attributed to biliary strictures or allograft dysfunction, and thus, the diagnostic workup is commonly directed towards these entities (30). This can potentially lead to a diagnostic delay. This particularly holds true for patients with primary sclerosing cholangitis (PSC), who are also at a higher risk of developing pancreatic adenocarcinoma than the general population (31). Although PSC was not the transplant diagnosis for any of the six patients in our study, these patients may potentially be in a higher risk of delayed cancer diagnosis, due to their high incidence of biliary complications (32). Our case series, as well as previously published cases, shows there is often a relatively long time between the LT surgery and diagnosis of pancreatic adenocarcinoma, emphasizing the importance of long-term follow-up in this patient population. The

Table 3 Previously published cases of pancreatic adenocarcinoma after liver transplantation

First author, year	LT diagnosis	Age (years)/sex	Interval between LT and diagnosis	Tumor size on imaging (cm)	Management	Last disease extent	Status	Survival after diagnosis
Abbasoglu, 1997, (26)	NA	NA	NA	NA	NA	NA	Died	NA
Kelly, 1998, (27)	NA	66/NA	2 years	NA	NA	NA	Died	1 month
Stauffer, 2009, (25)	Alpha-1 antitrypsin deficiency	56/M	3.8 years	>4	Resection	Disease-free → recurrence	NA	21 months
Sutcliffe, 2010, (28)	PSC	40/M	3 years	3	Resection + chemotherapy	Disease-free locoregional recurrence with retroperitoneal lymphadenopathy	Dead	10 months
Ester, 2018, (5)	HCV	66/M	1–2 years	4	Palliative chemotherapy	Progression with compression and dilation of biliary system	NA	NA
Kobayashi, 2018, (29)	Alcoholic liver disease	59/F	4 years	NA	Chemotherapy	Progression	Died	4 months
	HCV	60/M	13 years	NA	Resection	Lymph node metastasis → peritoneal dissemination	Died	4 months

HCV, hepatitis C virus; LT, liver transplantation; M, male; NA, not available; PSC, primary sclerosing cholangitis.

overlap in clinical presentation and laboratory data abnormalities of pancreatic adenocarcinoma and LT complications requires ongoing vigilance, especially in patients with unexplained hyperbilirubinemia and history of tobacco and/or alcohol use, to prevent this potential delay in diagnosis and management.

When a patient is diagnosed with resectable pancreatic post-LT, the prior transplant and immunosuppression will render pancreatic resection and postoperative recovery more complex and challenging. The anatomy of the hepatoduodenal ligament is altered during the LT, making it technically more challenging to perform pancreaticoduodenectomy without harming the liver allograft. Knowledge and familiarity with a patient's LT anatomy and the surgeon's experience in dealing with reoperation scenarios after LT are of utmost importance. Anastomotic leak is a relatively common complication after pancreaticoduodenectomy (33), and the immunosuppressive state in LT recipients only increases this risk. Additionally, higher dose of tacrolimus has been associated with increased risk for post-LT solid organ malignancy (34). Data suggest that LT recipients on tacrolimus-based immunosuppression demonstrated a two-fold higher risk of *de novo* malignancy post-LT compared to LT recipients on cyclosporine-based immunosuppression (35). Further multi-center studies are required to unveil whether decreasing or even halting immunosuppression in these patients may be sound. In many of these cases the immunosuppression regimen is likely already minimized because of the long time period between LT and development of pancreatic adenocarcinoma.

Certain limitations should be taken into consideration when interpreting the results of our study. One of these is the retrospective, single-center nature of our study. The small size of our study population may also preclude generalization of our results to other populations. Additionally, there may be LT recipients who were transplanted at our center but may have been later diagnosed with pancreatic adenocarcinoma in other centers that we could not identify and include in our analysis.

In conclusion, although uncommon, there is an increased

incidence of pancreatic adenocarcinoma following LT when compared to the general population, with a long lag time between LT and development of pancreatic adenocarcinoma. Timely diagnosis requires long-term vigilance, and management requires expertise and familiarity with LT, pancreatic resection, and immunosuppression management.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://dx.doi.org/10.21037/apc-21-4

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apc-21-4). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Vanderbilt University Medical Center Institutional Board Review (IRB#192061) and individual consent for this retrospective analysis was waived.

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