

# Long-term outcomes of living donor liver transplantation in patients with a prior history of nonhepatic malignancy

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**SUMMARY** Posttransplant malignancy has become a significant cause of mortality. Data on the long-term outcomes of patients with pretransplant nonhepatic malignancy (PTM) after living donor liver transplantation (LDLT) are scarce, although the recipients of other organs with PTM have been reported to have a poor survival. Fifteen patients with PTM (4.4%) among the 342 adult recipients were identified in our LDLT programs. The outcomes of the patients with PTM after LDLT were compared to those of patients without PTM in terms of the all-cause mortality and cancer-specific mortality (defined as mortality related to malignancy except for hepatocellular carcinoma, cholangiocarcinoma, or neuroendocrine tumor). The sites of PTM included the breast in six, stomach in two, and colon, lung, kidney, uterine, thyroid, larynx, and acute myelogenous leukemia in one each. The median interval from the PTM treatment to LDLT was 57 months (range, 2-298). The patients who received the curative treatment for PTM were selected as the recipients. No patients with PTM had recurrence during the follow-up period. The 1-, 5-, and 10-year patient survival rates were 100%, 92.9%, and 92.9% in the PTM group and 86.2%, 76.7%, and 68.5% in the non-PTM group, respectively ( $p = 0.142$ ). Likewise, there was no significant difference between the two groups in the cancer-specific mortality. In conclusion, the patients with PTM had comparable outcomes with regard to mortality and cancer-specific mortality compared with those without PTM. This study showed that the patients with PTM can obtain an acceptable outcome after LDLT when carefully selected.

**Keywords** pretransplant malignancy, living donor liver transplantation, all-cause mortality, cancer-specific mortality

## 1. Introduction

The survival in liver transplantation (LT) has improved significantly over time. The age of the recipients has increased steadily (1,2), and it is expected that more patients might have a history of pretransplant nonhepatic malignancy (PTM).

Solid organ transplant recipients are at an increased risk for the development of posttransplant malignancies including the recurrence of PTM and *de novo* malignancy due to the immunosuppression, compared with the general population (3-8). Cancer after transplantation causes considerable morbidity and mortality. There are some reports that PTM is a relative contraindication to solid organ transplantation (9,10). Organ transplantation for patients with PTM has been described from renal experiences (11-21). In addition, there are several reports describing about the outcomes of LT in patients with

PTM (22-25), however, there are no reports on the outcomes after living donor LT (LDLT).

The present study explored the clinical outcomes, including cancer recurrence, in LDLT patients with PTM.

## 2. Patients and Methods

### 2.1. Patients and study design

A total of 342 adult patients with end-stage liver disease who underwent LDLT at Kumamoto University Hospital from January 1999 to December 2018 were enrolled in this study. Fifteen patients with PTM were identified retrospectively. Data were collected on patient characteristics, pre-LDLT malignancy, treatment, and post-LDLT recurrence by a clinical examination. The all-cause mortality was examined

as the patient survival. In addition, the cancer-specific mortality (defined as death related to the recurrence of PTM, and *de novo* malignancy; all other deaths, including those from recurrence of hepatocellular carcinoma [HCC], intrahepatic cholangiocarcinoma, and neuroendocrine tumor liver metastases identified before LDLT, were censored) was investigated in the patients with and without PTM ( $n = 327$ ).

This study was conducted in accordance with the Declaration of Helsinki after approval from our institutional ethics board. Written informed consent was obtained from all patients.

## 2.2. Selection for LDLT

The patients with PTM were considered as LDLT candidates when all of the following factors were satisfied: (1) Patients had received the curative treatment for PTM, and (2) the expected 5-year survival rate related to PTM after treatment was 70-80% or greater.

## 2.3. Immunosuppression

Basic immunosuppressants included tacrolimus and steroid after LDLT. The immunosuppression regimen for the patients with PTM was indicated as the same standard regimen used for the patients without PTM. All patients began tacrolimus within 24 h after graft perfusion. Target trough levels of tacrolimus were 10 to 15 ng/mL during the second week postoperatively and then around 10 ng/mL during the first month postoperatively, 5 to 10 ng/mL until 3 months, and around 5 ng/mL thereafter. Steroids were given with tapering within 3 months (methylprednisolone 1 mg/kg/day 1-3 days after operation and 0.5 mg/kg/day 4-6 days and 0.3 mg/kg/day 7 day and prednisone 0.3 mg/kg/day in the first month and then tapered). If acute

cellular rejection was diagnosed, patients were treated with bolus dose steroids followed by a tapered dose or the addition of mycophenolate mofetil.

## 2.4. Statistical analysis

The values were presented as the median and range. The Kruskal-Wallis test was applied respectively for paired and unpaired multiple comparisons. The Mann-Whitney test was applied respectively for paired and unpaired comparisons between two groups. The correlation of the categorical data and numerical data was evaluated using the chi-square test and Spearman's test, respectively. Cumulative survival rates were calculated using the Kaplan-Meier method, and differences between curves were evaluated using the log-rank test. A  $P$ -value  $< 0.05$  was recognized as significant. All statistical analyses were performed using the SPSS ver. 18 statistical software program (IBM, Tokyo, Japan).

## 3. Results

### 3.1. Patient's characteristics

Of the 342 patients, 15 (4.4 %) were found to have PTM before LDLT (Table 1). The underlying liver diseases for transplantation included hepatitis C virus-related liver cirrhosis (LC) ( $n = 7$ ), hepatitis B virus-related LC ( $n = 1$ ), alcoholic LC ( $n = 1$ ), primary biliary cirrhosis ( $n = 1$ ), nonalcoholic steatohepatitis ( $n = 1$ ), cryptogenic LC ( $n = 1$ ), secondary sclerosing cholangitis ( $n = 1$ ), idiopathic portal hypertension ( $n = 1$ ), and Budd-Chiari syndrome ( $n = 1$ ). Eight of these patients had HCC. The median age at LDLT was 60 years old (range, 45-69 years old) and the median Model for End-stage Liver Disease (MELD) score was 17.0 was (range, 8.0-27.0). The median age at the time of the cancer diagnosis was

**Table 1. Characteristics of LT patients with preexisting nonhepatic malignancy**

Patient No.	Age at transplant (years)	gender	Liver disease	MELD score	Age at malignancy (years)
1	54	M	HBV-LC	20	54
2	57	F	SSC	17	52
3	66	F	cryptogenic LC, HCC	13	66
4	55	F	HCV-LC, HCC	9	37
5	66	M	HCV-LC, HCC	10	51
6	68	M	HCV-LC, HCC	8	65
7	65	M	ALC, HCC	19	63
8	62	M	IPH	17	48
9	59	F	HCV-LC	27	42
10	69	F	HCV-LC, HCC	8	52
11	57	F	HCV-LC	21	48
12	55	F	PBC	19	51
13	60	F	NASH, HCC	14	56
14	62	F	Budd-Chiari syndrome	9	61
15	45	M	HCV-LC, HCC	17	20

LT, liver transplantation; MELD, Model for end-stage liver disease; SCC, secondary sclerosing cholangitis; HBV- and HCV-LC, hepatitis B and hepatitis C-related liver cirrhosis; HCC, hepatocellular carcinoma; ALC, alcoholic liver cirrhosis; IPH, idiopathic portal hypertension; PBC, primary biliary cirrhosis; NASH, nonalcoholic steatohepatitis.

**Table 2. Clinical data on LT patients with preexisting nonhepatic malignancy**

Patient No.	Malignancy	Type/stage	Treatment	Interval to LT (months)	Follow-up post LT (months)	Tumor Recurrence	Survival
1	Larynx	T1N0M0(stage I)	Radiation	2	68	No	Alive
2	Thyroid	n.a.	Right lobectomy	57	98	No	Alive
3	Lung	T1aN0M0(stage IA)	Resection	3	76	No	Alive
4	Uterine	CIS	Hysterectomy	216	136	No	Alive
5	Stomach	T1aN0M0(stage IA)	Endoscopic resection	192	59	No	Alive
6	Stomach	T1aN0M0(stage IA)	Endoscopic resection	36	20	No	Dead
7	Colon	T3N1M0(stage IIIA)	Resection+Chemotherapy	19	27	No	Alive
8	Kidney	T1aN0M0(stage IA)	Nephrectomy	165	43	No	Alive
9	Breast	n.a.	Mastectomy	204	63	No	Alive
10	Breast	n.a.	Mastectomy	204	57	No	Alive
11	Breast	T3N2M0(stage IIIA)	Mastectomy+Radiation +Chemotherapy	115	92	No	Alive
12	Breast	T2N1M0(stage IIB)	Mastectomy	51	58	No	Alive
13	Breast	T2N0M0(stage IIA)	Mastectomy+Radiation	48	44	No	Alive
14	Breast	T2N0M0(stage IIA)	Mastectomy+Chemotherapy	9	7	No	Alive
15	AML	n.a.	Chemotherapy	298	77	No	Alive

LT, liver transplantation; CIS, carcinoma in situ; AML, acute myelogenous leukemia

52 years old (range, 20-66 years old). Six patients were male, and nine were female.

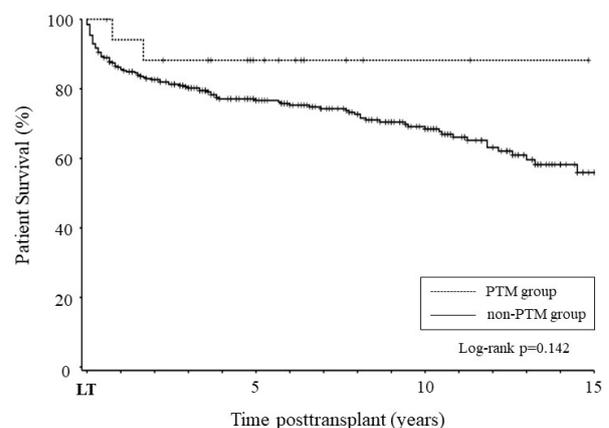
The PTM consisted of a total of 15 cancers: breast cancer ( $n = 6$ ), gastric cancer ( $n = 2$ ), colon cancer ( $n = 1$ ), thyroid cancer ( $n = 1$ ), laryngeal cancer ( $n = 1$ ), lung cancer ( $n = 1$ ), renal cancer ( $n = 1$ ), uterus cancer ( $n = 1$ ), and acute myelogenous leukemia (AML) ( $n = 1$ ).

### 3.2. Pretransplant cancer status

The median interval from treatment of cancer to LDLT was 57 months (range, 2-298 months) (Table 2). Laryngeal and lung cancer were found during the pretransplant examination. Because the liver function in the patients with laryngeal and lung cancer were considered to be stable enough to postpone transplantation, they underwent LDLT two and three months later, respectively, following treatment for their early-stage cancers (laryngeal cancer/stage I, lung cancer/stage IA). Two patients with gastric mucosal cancer underwent radical endoscopic mucosal resection (EMR) and received LDLT at more than three years after EMR. The deteriorated liver function of the patient with advanced colon cancer did not allow us to delay transplantation and this patient underwent LDLT 19 months after the curative treatment for cancer. In the patients with breast cancer, the median interval between the treatment and LDLT was 83 months (range, 9-204 months). The patient with AML underwent LDLT over 20 years after achieving a complete response with chemotherapy. No patients with PTM experienced recurrence after primary treatment of cancer before LDLT.

### 3.3. Immunosuppression and rejection after LDLT

Primary immunosuppression consisted of tacrolimus and steroids in all the patients. Mycophenolate mofetil



**Figure 1. The cumulative patient survival following liver transplantation.**

was added in seven patients. No patients developed rejection that required steroid bolus therapy.

### 3.4. Posttransplant outcomes

No patients with PTM experienced recurrence for a median follow-up of 59 months (range, 8-136 months) after LDLT. One of the 15 PTM patients (6.7%) died during the follow-up periods due to sepsis 20 months after transplantation, an event that was not related to PTM. A total of 98 of the 327 non-PTM patients (30%) died during the follow-up period. The 1-, 3-, and 5-year patient survival rates were 100%, 92.9%, and 92.9% in the PTM group and 86.2%, 80.2%, and 76.7% in the non-PTM group, respectively, without a statistically significant difference ( $p = 0.142$ ; Figure 1). No patients died of *de novo* malignancy or PTM recurrence in the PTM group, while eight died of *de novo* malignancy in the non-PTM group. There was no significant difference in the cancer-specific mortality rate between the two groups ( $p = 0.251$ ).

#### 4. Discussion

In this study, we identified the 15 patients with PTM (4.4%). This study showed that selected patients with PTM were suitable as LDLT candidates because the recurrence rate of the PTM was low. If the 5-year survival rates related to PTM after curative treatment are expected to be 70-80% or more, regardless of early or advanced cancer, LDLT might be considered, irrespective of the cancer-free interval and cancer type. From this perspective, it is necessary to hold multidisciplinary discussions about the indication of LDLT among hepatologists, transplant surgeons, and oncologists. This is the first report to describe the long-term outcomes of patients with PTM after LDLT.

In renal transplantation, the recurrence rate of PTM ranged from 13.7% to 22% (12,17,18,20,26). Penn et al. reported that almost of these recurrences occurred in the first 2 years after transplantation (12). In the previous literature, which was limited in number, the recurrence rate of the PTM after LT ranged from 2.7% to 13.8% (22-25). The median duration from LT to the time of diagnosis of the recurrence of the PMT was 12 months (range, 6-36) (22-25). In our study, no recurrence of PTM developed for a median follow-up of 59 months (range, 8-136) after LDLT.

The optimal cancer-free interval between the treatment of cancer and transplantation has not yet been established. Some reports showed that the shorter cancer-free intervals were associated with a higher risk of cancer recurrence and cancer-specific mortality (12,27,28). Sigurdardottir *et al.* reported that a cancer-free survival for  $\geq 5$  years before the transplantation was associated with the lowest risk of recurrence in lung and heart transplantation (27). In addition, a minimum of two-year waiting period until transplantation has been recommended in some guidelines of renal transplantation, based on the understanding that recurrence tends to occur within two years of treatment in general (11,28,29).

However, others have found no association between the cancer-free interval and recurrent cancer mortality. Dahle *et al.* showed that short waiting periods between treatment of pretransplant cancer and transplantation were not associated with recurrent cancer or all-cause mortality (18). Acuna *et al.* reported that there was no association between prolonged remission times before transplantation and a reduced risk of recurrence or death from malignancy (17). Similarly, we found no association between a prolonged cancer-free period and posttransplant cancer recurrence. In LT, it is difficult to postpone the timing of transplantation because of there is no other alternative treatment for liver failure.

The guidelines in renal transplantation recommend waiting two years after cancer remission in case of low-risk malignancy (*i.e.* prostate, thyroid, testicular, renal cancer). For colorectal cancer, the interval between cancer remission and transplantation was suggested to

be 0-5 years (depending on the stage) by the American society of Transplant Physicians (AST) and over 5 years by the European Best Practice Guidelines (EBPG) for Renal Transplantation, respectively (29,30). The interval between cancer remission and transplantation of breast cancer was recommended to be 2-5 years by the AST and over 3 years by the EBPG. For malignant melanoma, the interval was recommended to be 2-5 years by the AST and over 2 years by the EBPG (29,30). In our series, almost all patients had early or low TMN (stage I-II) stage of each malignancy. Although three patients with an early TMN (stage I-II) stage underwent LT within one year from cancer treatment in our series, no recurrence occurred. The intervals from PTM treatment to LT in the patients with advanced-stage colon cancer and breast cancer was 19 months and 9 years, and neither has experienced recurrence during the follow-up period. 5-year disease free survival rate in the patients with Stage IIIA colon cancer which was curatively resected and received chemotherapy was over 70% in the literature (31,32). We accepted the patient with advanced colon cancer as the candidate of transplant recipient.

PTM is reportedly associated with an increased risk of all-cause mortality and cancer-specific mortality, including PTM recurrence and *de novo* malignancies after transplantation, compared to those without PTM, especially case of heart and renal transplantation (17,26,28,33,34). However, the findings of other studies as well as our own work were not compatible with this observation (18,35). Viecelli *et al.* reported that a history of malignancy did not have an additive effect on the all-cause mortality or cancer-specific mortality in the large cohort (35). In contrast, we found that the all-cause mortality and cancer-specific mortality in the patients with PTM were comparable to those in the patients without PTM in our study.

Two limitations associated with our study deserve further comment: namely, the retrospective nature and small sample size. Ideally, prospective and multicenter studies, or otherwise meta-analyses given the rarity of disease are therefore needed in order to clarify the indication of LDLT while taking into consideration the cancer type, cancer stage, and interval between the treatment of PTM and LDLT. Despite these limitations, we believe that this study provides useful information regarding the clinical outcomes of patients with PTM after LDLT.

In conclusion, the recurrence rate of PTM after LDLT is low, and PTM is not associated with an increased risk of all-cause mortality or cancer-specific mortality. The results of our study suggest that patients with PTM can be considered as candidates for LDLT if appropriately selected.

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