Surgical Treatment and Outcome of Patients with *De Novo* Lung Cancer After Liver Transplantation

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Abstract. *Background: De novo malignancy, including primary lung cancer, is one of the limitations to long-term survival after liver transplantation. The purpose of this study was to describe patients who developed de novo lung cancer after living-donor liver transplantation (LDLT) and investigate their clinicopathological features as well as the feasibility of surgical resection. Patients and Methods: We investigated 554 patients who underwent LDLT. Results: De novo lung cancer after LDLT was observed in five (0.9%) out of 554 studied patients: four men and one woman, aged 61-78 years (mean=67 years). All four men had a smoking history. Clinical stages of de novo lung cancer were stage IA in three patients, and stage IB and IV in one patient each. Three out of five patients underwent pulmonary lobectomy and pathological stage was IA in two patients and IIA in one. All patients who underwent surgery stopped immunosuppressive therapy 1 day preoperatively and restarted on postoperative day 1. There were no serious postoperative complications. All three patients are still alive without any recurrence, with survival ranging from 8 to 29 months, with an average of 16.3 months after diagnosis of lung cancer. Conclusion: Although the study population was small, these results suggest that pulmonary lobectomy of de novo lung cancer after LDLT, even under immunosuppressive conditions, is a feasible procedure and may yield a survival benefit.*

Liver transplantation (LT) is a definite therapy for patients with end-stage liver diseases. Recipients of LT have a good prognosis, thus the number of long-term survivors has

increased (1). However, the increased incidence of *de novo* malignancy, including primary lung cancer, is one of the limitations to long-term survival after LT. Lung cancer is the leading cause of cancer-related death worldwide and is the most frequent type of solid organ cancer after LT (2). Surgical treatment for *de novo* malignancy after LT is an important consideration because an increase in the incidence of cancer in immunocompromised patients has been observed (3). However, the treatment for these diseases is limited by immunosuppressive therapy necessary after LT. Thus, it is necessary to evaluate the treatment of *de novo* lung cancer, especially surgical resection, after LT. Only a few reports discuss surgery for *de novo* lung cancer after LT, including postoperative course and surgical outcomes. Therefore, the aim of this study was to describe patients who developed *de novo* lung cancer after LT and demonstrate the feasibility of surgical resection.

Patients and Methods

This study was approved by the Ethics Committee of the Kyushu University Hospital, and written informed consent was obtained from all patients. A total of 554 consecutive patients underwent living-donor LT (LDLT) at Kyushu University Hospital from May 1997 to December 2012. There were 255 men and 299 women, aged 18-74 years (mean=52 years). The indications for LDLT were hepatocellular carcinoma (HCC) in 165 patients, liver cirrhosis (LC) in 113, primary biliary cirrhosis (PBC) in 81, fulminant hepatic failure in 54, alcoholic cirrhosis in 21, primary sclerosing cholangitis in 19, non-alcoholic steatohepatitis in 16, auto-immune hepatitis in 14, biliary atresia in seven, Wilson's disease in five, and other causes in 59. The indications for LDLT in the Kyushu University Hospital include HCC with neither extrahepatic metastasis nor macroscopic vascular invasion in conventional imaging studies. No limitations were set regarding the size and number of tumours. The pre-transplant work-up for HCC consisted of a combination of ultrasonography, dynamic computed tomographic (CT) scans, magnetic resonance imaging, CT angiography and CT during arteriography, where possible. Patients with extrahepatic metastasis were excluded by head and chest CT scans, bone scintigraphy and positron-emission tomography. Adjuvant chemotherapy and immunosuppressive therapy were previously described (4).

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After LDLT, immunosuppression was initiated. All patients received immunosuppressive therapy with a combination of cyclosporine A (Neoral), mycophenolate mofetil (CellCept), tacrolimus and prednisolone (Predonine). Patients were routinely evaluated as follows. Post-transplant follow-up consisted of abdominal and chest CT, bone scintigraphy and positron-emission tomography imaging studies at 3-month intervals during the first year and yearly thereafter. Tumour markers were checked monthly during the first year and at 3-month intervals thereafter.

Results

Frequency and clinicopathological features of *de novo* lung cancer after LDLT. The average follow-up was 56 months (range=0-207 months) and 438 (79.1%) patients are currently still living. The actuarial overall 1-, 3-, 5- and 10-year survival rates were 88.1, 82.6, 79.4 and 71.9%, respectively (Figure 1).

***De novo* lung cancer after LDLT** was observed in five (0.9%) out of 554 patients (Table I): four men and one woman, aged 61-78 years (mean=67 years). Three of these patients underwent LDLT for HCC and one each for PBC and end-stage hepatitis-C-related LC. Four patients were screened for *de novo* lung cancer routinely and one because of dyspnoea. The four men had a history of smoking. The average interval between LDLT and diagnosis of *de novo* lung cancer was 78 months (range=0-162 months). Immunosuppressive drugs immediately before treatment of *de novo* lung cancer were as follows: tacrolimus in two patients and cyclosporine A with/without mycophenolate mofetil in three patients. Clinical stage of *de novo* lung cancer was IA in three patients and IB and IV in one patient each.

Treatment of patients with *de novo* lung cancer after LDLT. Treatment of the five patients with *de novo* lung cancer is shown in Table II. Primary tumours were located in the left upper lobe in two patients and right lower lobe in three. Pathological type of *de novo* lung cancer was adenocarcinoma and squamous cell carcinoma in two patients each, and unknown in the other patient. Three patients underwent surgical resection. Contraindications for surgery were as follows. Patient 1 had adenocarcinoma with malignant effusion and multiple pulmonary metastases; patient 2 had both clinical stage IB non-small cell lung cancer and unresectable advanced maxillary cancer. Therefore, patient 1 received best supportive care and patient 2 radiotherapy.

Patients undergoing pulmonary resection after LDLT. Table III shows the surgical outcome of the three patients who underwent pulmonary resection. The average tumour size was 14.7 mm (range=13-17 mm). Patients 4 and 5 underwent right lower lobectomy and patient 3 left upper lobectomy. Patient 3 underwent pulmonary resection 3 months after LDLT,

Figure 1. Overall survival curve for patients receiving living donor liver transplantation (LDLT).

because *de novo* lung cancer was synchronously discovered with LC. The average operating time was 270 minutes (range=236-313 minutes) and the average amount of blood loss was 82 g (range=0-140 g). The postoperative course of the three patients is also shown in Table III. All the patients stopped immunosuppressive therapy 1 day preoperatively and restarted on postoperative day (POD)1. In all patients, the thoracic tube was removed within 5 POD (average=3.6 POD, range=2-5 POD). There were no serious complications and the average hospital stay was 9.7 days (range=7-15 days).

Outcome of patients with *de novo* lung cancer after LDLT. Treatment and outcome of patients with *de novo* lung cancer after LDLT are shown in Table IV. *De novo* lung cancer was pathologically confirmed as stage IA in two patients and IIA in one patient. All three patients that underwent surgical resection are still alive, although the other two patients that were unable to undergo surgery died. The survival range for the patients who underwent surgical resection was 29-174 months (mean=122 months) after LDLT. In contrast, the survival range for the patients who were unable to undergo surgical resection was 33-57 months (mean=45 months) after LDLT. In addition, the survival range for the patients who underwent surgical resection was 8-29 months (mean=16 months) after diagnosis of *de novo* lung cancer.

Discussion

There is an increased risk of *de novo* cancer in patients after LT because post-transplant survival has dramatically improved. *De novo* malignancy after LT remains the leading cause of late death, significantly impairing long-term survival

Table I. Clinical features of patients with *de novo* lung cancer after living-donor liver transplantation (LDLT).

Patient no.	Gender	Age (years)	Reason for screening	Smoking status	Liver disease	Immunosuppression	Interval between LDLT and diagnosis of <i>de novo</i> lung cancer
1	Male	67	Dyspnoea	Former	PBC	Tacrolimus	33
2	Male	65	RS	Former	HCC	Cyclosporine A	39
3	Female	67	RS	Non	LC	Cyclosporine A+mycophenolate mofetil	0
4	Male	61	RS	Former	HCC	Tacrolimus	162
5	Male	78	RS	Former	HCC	Cyclosporine A	156

HCC: Hepatocellular carcinoma; LC: liver cirrhosis (end-stage hepatitis C-related); PBC: primary biliary cirrhosis; RS: routine screening.

Table II. Clinicopathological features and treatment of patients with *de novo* lung cancer after living-donor liver transplantation.

Patient no.	Primary site	Pathological type	Clinical stage	Treatment
1	RLL	Adenocarcinoma	IV	Best supportive care
2	LUL	Unknown	IB	Radiotherapy
3	LUL	Adenocarcinoma	IA	Surgery
4	RLL	Squamous cell carcinoma	IA	Surgery
5	RLL	Squamous cell carcinoma	IA	Surgery

HCC: Hepatocellular carcinoma; LUL: left upper lobe; RLL: right lower lobe.

(2). The risk of *de novo* cancer increases with age and time after LT. Desai *et al.* showed that the standardised incidence ratio for all cancers after LT was 2- to 3-fold compared to the general population adjusted for age, gender and year (5).

The most common site for developing *de novo* solid organ malignancies after LT is the lungs (2). It was shown that 824 out of 89,036 (0.925%) LT patients developed *de novo* lung cancer (2). Recent small studies have also revealed that the incidence rate of primary lung cancer after LT is 0.3-0.8% (8-10). The frequency (five out of 544 patients, 0.9%) of *de novo* lung cancer in the current study was similar to that in previous studies.

Previous studies have shown that the time to diagnosis of *de novo* lung cancer was 47-71 months after LT (6-8). Moreover, Zhou *et al.* showed that cancer risk was increased at 1 year after LT, gradually increasing and reaching a peak at 6-10 years of follow-up, and that during the first 6 months and >16 years after LT, cancer risk decreased (2). Our mean time to diagnosis of 78 months is similar to that in previous studies.

Smoking is a risk factor of *de novo* lung cancer after LT (13, 14). Mangus *et al.* reported that the incidence of *de novo* cancer was higher for patients with, compared to those without a history of smoking (15). In the present study, all four male patients also had a history of smoking.

The major cause of the development of *de novo* malignancy is related to the loss of immunovigilance induced by immunosuppressive drugs (16). The risk of *de novo*

Table III. Surgical treatment of patients with *de novo* lung cancer after living-donor liver transplantation. All patients discontinued immunosuppressive drug use one day prior to surgery and recommenced it one day after surgery.

Patient no.	Surgical procedure	Chest drain removal (POD)	Hospital stay (days)
3	LUL	5	15
4	RLL	2	7
5	RLL	4	10

LUL: Left upper lobectomy; RLL: right lower lobectomy, POD: postoperative day.

cancer can be reduced by simple lifestyle changes, including smoking cessation, as well as maintaining minimum exposure to immunosuppression (17). Thus, LT patients with a history of smoking might benefit from careful post-LT surveillance for *de novo* cancer, although our small study cannot lead to any such definitive conclusion.

In the present study, *de novo* lung cancer was stage IA in three patients and IB and IV in one patient each. Stage I *de novo* lung cancer in these patients was detected by routine screening, which therefore detects post-LT cancer at an early stage, leading to surgical resection and improved survival. Unfortunately, patient 2 was found to have unresectable advanced maxillary cancer at the same time (double *de novo* cancer).

Table IV. Outcome of patients with *de novo* lung cancer after living-donor liver transplantation (LDLT).

Patient no.	Pathological stage	Survival after LDLT (months)	Survival after diagnosis of <i>de novo</i> lung cancer (months)	Status
1	-	33	0	Dead
2	-	57	25	Dead
3	IA	29	29	Alive
4	IIA	174	12	Alive
5	IA	163	8	Alive

There is no definite consensus regarding timing for discontinuation or restarting immunosuppressive drugs in LDLT patients undergoing surgery. In the present study, all patients undergoing surgery stopped their immunosuppressive therapy 1 day preoperatively and restarted on POD1, as previously reported (9). Consequently, there were no serious postoperative complications. All three patients are still alive and survival range was 6-29 months (mean=15.7 months) after diagnosis of lung cancer. The other two patients died from *de novo* cancer.

We previously reported the results of surgical resection of pulmonary malignant tumours, including recurrence and *de novo* malignancy, such as primary lung cancer or mucosa-associated lymphoid tissue lymphoma, after LDLT (9). However, we did not experience any operable cases of *de novo* lung cancer in that study. In addition, none of patients with tumour recurrence underwent pulmonary lobectomy, only limited surgery such as wedge resection. Only a few studies have reported surgical resection of *de novo* lung cancer after LT (10, 11). Jiménez *et al.* reported that one patient with stage IIIB primary lung cancer received exploratory thoracotomy and one with stage IA primary lung cancer underwent a curative operation (10). Another study reported pulmonary wedge resection in a patient with stage IA pulmonary adenocarcinoma (11). Therefore, it is unclear whether major lung resection, including lobectomy, which is considered the standard procedure for primary lung cancer, would be feasible for LDLT patients. We previously reported a synchronous case with fatal LC and lung cancer (12). This case was successfully treated for LC by LDLT and pulmonary lobectomy for primary lung cancer was performed 3 months after LDLT. Moreover, we newly experienced two operable cases of *de novo* lung cancer after LDLT. As a result, we have seen five patients with *de novo* lung cancer, including three who underwent pulmonary lobectomy after LDLT. Thus, pulmonary lobectomy for *de novo* lung cancer after LDLT might be a safe and promising therapy in LDLT patients under immunosuppressive conditions.

In conclusion, although we included a small number of patients, we reported the frequency and surgical results of *de*

novo lung cancer after LDLT. These results suggest that pulmonary lobectomy of *de novo* lung cancer after LDLT is a safe and acceptable procedure and may benefit patients receiving LDLT.

Conflicts of Interest

None declared.

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