De novo Cancers Following Liver Transplantation: A Single Center Experience in China

Songfeng Yu1,2,3, Feng Gao1,2,3, Jun Yu1,2,3, Sheng Yan1,2,3, Jian Wu1,2,3, Min Zhang1,2,3, Weilin Wang1,2,3, Shusen Zheng1,2,3*

1 Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, 2 Key Laboratory of Combined Multi-Organ Transplantation, Ministry of Public Health, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, 3 Key Laboratory of Organ Transplantation, Zhejiang Province, Hangzhou, China

Abstract

Background: De novo cancers are a growing problem that has become one of the leading causes of late mortality after liver transplantation. The incidences and risk factors varied among literatures and fewer concerned the Eastern population.

Aims: The aim of this study was to examine the incidence and clinical features of de novo cancers after liver transplantation in a single Chinese center.

Methods: 569 patients who received liver transplantation and survived for more than 3 months in a single Chinese center were retrospectively reviewed.

Results: A total of 18 de novo cancers were diagnosed in 17 recipients (13 male and 4 female) after a mean of 41 ± 26 months, with an overall incidence of 3.2%, which was lower than that in Western people. Of these, 8 (3.32%) cases were from 241 recipients with malignant liver diseases before transplant, while 10 (3.05%) cases were from 328 recipients with benign diseases. The incidence rates were comparable, p = 0.86. Furthermore, 2 cases developed in 1 year, 5 cases in 3 years and 11 cases over 3 years. The most frequent cancers developed after liver transplantation were similar to those in the general Chinese population but had much higher incidence rates.

Conclusions: Liver transplant recipients were at increased risk for developing de novo cancers. The incidence rates and pattern of de novo cancers in Chinese population are different from Western people due to racial and social factors. Pre-transplant malignant condition had no relationship to de novo cancer. Exact risk factors need further studies.

Introduction

Liver transplantation (LTx) is the sole curative option for patients with end-stage liver diseases. With the improvement of immunosuppression and other refinements in the management of patients after LTx, graft and patient survivals have markedly increased. Many centers have reported the graft and patient survival rates over 90% for 1 year and close to 80% for 5 years [1]. Therefore, long-term complications after LTx become more important. Among these, development of cancers (recurrence or de novo) after LTx is a growing problem leading to an increased late mortality with a functioning graft [2].

Patients who underwent LTx for liver malignant diseases such as hepatocellular carcinoma (HCC) have a potential risk of disease recurrence post transplantation. Up to date, intensive studies have focused on tumor recurrence towards optimizing the candidate criteria and tumor surveillance in such population [3]. On the other hand, studies on de novo cancers after LTx in patients without pre-existing malignancies before LTx are rising. In recent years, several reports have clearly shown increased incidences of various types of de novo cancers following LTx [4–10]. Though mechanisms for the posttransplant de novo cancer remain unclear, the etiology is believed to be multifactorial. Immunosuppression is proposed to play a major role in the oncogenesis, both through impaired immunosurveillance and through direct carcinogenic effect of agents [11]. Other potential factors such as viral infection, longer survival, oncogene adoptive transfer from donors, age, gender et al could also be involved [12,13].

The reported incidence of developing de novo cancers ranged from 2.3 to 26%, depending on the demographics of the recipients, length of follow-up, and the era in which transplantations were performed [13,14]. The most common de novo cancers reported in literatures were skin cancers followed by posttransplantation lymphoproliferative disorder (PTLD) [13]. However, most of the studies were performed in Western countries. As the epidemiology of various cancers varies markedly in different
geographic eras and ethnic populations, for example skin cancer is relatively rare in Eastern people, we thus reviewed our series for the incidence and pattern of de novo cancers that might develop after LTx in Chinese population.

Materials and Methods

From a maintained database, we retrospectively reviewed all the patients who underwent orthotopic liver transplantation between January 2005 and December 2011 at the first affiliated hospital, school of medicine, Zhejiang university. Patients who survived at least 3 months after transplantation were enrolled in this study. Those who received combined organ transplantation or had previously undergone transplantation were excluded. Clinical data from patients who developed de novo cancers post transplantation were collected including primary diagnosis, immunosuppression regimen, type of cancer, elapse time from LTx to diagnosis of cancer, and patient survival. Ethical approval was obtained from the Committee of Ethics in Biomedical Research of Zhejiang University and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all participants.

The primary immunosuppression regimen consisted a triple regimen of tacrolimus (FK506) in combination with mycophenolate mofetil (MMF) and prednisolone for patients with benign end stage liver diseases. The dose of prednisolone was tapered to 5 mg daily 6 weeks post transplantation and was withdrawn after 3 months. Patients underwent LTx for HCC received an induce therapy with Basiliximab and steroid-free regimen. The target blood trough level of FK506 was 7–10 ng/ml for the first post-operative month and aimed at 5–7 ng/ml thereafter. MMF was discontinued when drug specific complications occurred. For some patients, FK 506 monotherapy was achieved after long time stable survival. All the patients were followed up weekly until stable, and then monthly, including regular monitoring biochemical parameters and drug concentration. Image surveillance was also conducted with ultrasound every month and computed tomography for abdomen and chest every half a year.

Data were express as mean value and standard deviation and analyzed with the statistical software package SPSS 15.0. Statistical analyses were carried out using the chi-square test (noncontinuous variables), Kaplan-Meier method with log-rank test (patient survival), Student’s t-test (continuous variables with normal distribution) and the Mann–Whitney U-test (continuous variables with nonparametric distribution). A p value < 0.05 was considered statistically significant.

Results

Risk factor for de novo cancers after LTx

During the study period, a total of 569 patients underwent LTx at our center and survived at least 3 months after transplantation were enrolled for the retrospective study. Out of the 569 patients (492 male and 77 female, mean age 47.4 ± 9.7 years), a total of 18 de novo cancers were diagnosed in 17 patients (13 male and 4 female) after a mean of 41 ± 26 months (8 to 85 months), with an overall incidence of 3.2%. Results from our series showed that female recipients were more likely to develop de novo cancer (4/77 vs. 13/492). Figure 1A shows the risk of de novo cancer after LTx were significantly higher in female than male (p = 0.015).

In general population, young adults have lower risk of tumor, and this risk increases with age. According to the patient age at transplantation, we divided the patients of our series into three groups: <40, 40–50 and >50 years. Although there was no significant difference for the risks of de novo cancer after LTx in three groups (p > 0.05), patients younger than 40 years seemed to have lower risk during late period after LTx than the elder patients (Figure 1B).

To determine whether pre-transplant malignant conditions could increase the incidence of de novo cancer after transplantation, 569 patients were divided into two groups. 241 patients were primarily diagnosed with malignant liver disease before LTx (malignant group), while 328 patients underwent LTx for benign end stage liver disease (non-malignant group). All the patients had no evidence of extrahepatic malignancies before LTx. The patients’ details and de novo cancer incidences for the two groups are listed in Table 1. There were differences in the patient ages and sex compositions between the two groups, with younger individuals and more males in the malignant group. For the types of LTx, patients in the malignant group underwent more cadaveric liver transplantation and less living donor liver transplantation than those in non-malignant group (90.9% and 9.1% vs. 72.6% and 27.4%, respectively). There were also significant differences in the follow-up time and patient survival rates between the two groups. Patients in the non-malignant group had longer follow-up time (32.7 ± 26.8 months vs. 37.1 ± 27.9 months) than those in the malignant group. There were 8 cases of de novo cancer developed in the malignant group and 10 cases in the non-malignant group. The incidence rates were comparable between the two groups (3.92% vs. 3.03%, p = 0.86) with an odds ratio 0.92. Hazard plots showed pre-transplant tumor status had no influence on the risks of de novo cancer after LTx (Figure 1C).

There was also no difference for the elapse time from LTx to de novo cancer between the two groups (44.0 ± 24.9 months vs. 44.5 ± 29.0 months, p = 0.97).

Prevalence of de novo cancers after LTx

Among the 18 de novo cancers, twelve types were identified. The most developed de novo cancer was PTLD (n = 3), followed by cancers in liver, stomach, lung, and cervix with 2 cases of each. Other less frequent cancers identified were pancreatic cancer, renal cancer, acute myeloid leukemia (M2a), myelodysplastic syndromes-refractory anemia with excess blasts (MDS-RAEB) and nasopharyngeal cancer. In addition, one patient presented a huge mass in the abdominal wall after a long-term incision infection due to anastomotic fistula of cholangiojejunostomy. Biopsy only showed poorly differentiated adenoscarcinoma infiltrating in the fibrous tissue of abdominal wall but did not identify its origin. She died 6 months after diagnosis lacking effective treatment. The patient who developed nasopharyngeal cancer also developed lung cancer 2 years later and died from complications of lung cancer. Most of the patients received one or two aggressive treatments including operation, chemotherapy, and radiotherapy. Over a mean follow-up period of 21.4 ± 21.0 months (range 1 to 89) after diagnosis of de novo cancers, 8 patients (47.1%) died. The causes of death were all related to the de novo cancers. The median survival time was 14 months. The demographic and clinical features of these patients are shown in Table 2.

According to the report of cancer incidences in China from 2003 to 2007 [15], the most frequent de novo cancers in the LTx recipient were similar to the most cancers developed in the general Chinese population. Furthermore, as summarized in Table 3, the incidence rates of either overall or most common cancers were much higher in LTx recipients, suggesting a higher relative risk of cancers following LTx than in the general population.
De novo cancers increase late mortality in LTx recipients

Further analysis for the elapse time from LTx to de novo cancer showed 2 cases developed in 1 year, 5 cases in 3 years and 11 cases over 3 years, indicating the incidence of de novo cancer increased as the patient survival accrued after LTx (Figure 2). To determine the role of de novo cancers in the causes of patient death after LTx, we excluded those who died of tumor recurrence, as which has been considered a major cause of death after LTx for patient with malignant liver disease. Kaplan-Meier survival analysis showed that patients with de novo cancers had significantly lower survival than the control patients after excluding those who died of tumor recurrence (p = 0.009, Figure 3). This suggests that compared with non-tumor factors de novo cancer has contributed more to the patient later mortality after LTx.

De novo cancers increase late mortality in LTx recipients

Discussion

In our series involving 569 patients of LTx over a 6 years period, de novo cancers were developed in 3.2% of patients at a mean interval of 41 months from the time of LTx. This incidence was among the lowest reported rate from the previous literatures. The highest incidence of posttransplant cancer was reported by a Spanish group, a rate of 26% (49 cases) in a cohort of 187 LTx recipients [16]. Baccarani et al from Italy reported an incidence of 10.3% of de novo malignancies in a series of 417 LTx patients survived for more than 30 days and without a previous diagnosis of cancer [4]. A larger series from a single center study by Jain et al in USA showed 6% of 1,127 LTx patients developed de novo cancers with a mean follow-up period of 34.1 months [8]. More recently, a 20-year experience from a single European center reported 71 (9.5%) out of 742 patients developed de novo neoplasm at a mean time period of 5 years after LTx [5]. Another similar single center
Table 1. Clinical details and de novo cancer incidences in recipients who underwent LTx for primary diagnosis of malignant and non-malignant disease.

|                         | Malignant group | Non-malignant group | P value |
|-------------------------|-----------------|---------------------|---------|
| No. of patients         | 241             | 328                 |         |
| Gender                  |                 |                     |         |
| Male                    | 219             | 273                 | 0.009   |
| Female                  | 22              | 55                  |         |
| Age (yr)                | 45.5±9.9        | 49.9±8.9            | <0.001  |
| Type of LTx             |                 |                     |         |
| Cadaveric               | 201 (90.9%)     | 238 (72.6%)         | 0.002   |
| LDLT                    | 40 (9.1%)       | 90 (27.4%)          |         |
| Follow-up (mo)          | 37.1±27.9       | 52.7±26.8           | <0.001  |
| No. of de novo cancers  | 8 (3.32%)       | 10 (3.05%)          | 0.86    |
| Elapse time from LTx to cancer (mo) | 44.0±24.9 | 44.5±29.0 | 0.97    |

LTx, liver transplantation; LDLT, living donor liver transplantation. Follow up time and age are expressed as the mean±SD.

Table 2. Demographic and clinical features of the patients with de novo malignancy.

| Patient No. | Sex/Age | Primary diagnosis | Type of LTx | Immuno-suppression | De novo malignancy | Time of occur (m)* | Treatment | Follow-up (m)# | Status |
|-------------|---------|-------------------|-------------|--------------------|--------------------|--------------------|------------|---------------|--------|
| 1           | M/50    | HCC               | Cadaveric   | FK+MMF             | PTLD               | 24                 | CTx+RTx    | 4             | Dead   |
| 2           | M/43    | HBV LC            | Cadaveric   | FK                 | PTLD               | 43                 | None       | 1             | Dead   |
| 3           | M/49    | HBV LC            | Cadaveric   | FK                 | PTLD               | 12                 | OP+CTx     | 89            | Alive  |
| 4           | F/60    | HCC               | Cadaveric   | FK                 | MDS-RAEB           | 37                 | None       | 3             | Dead   |
| 5           | M/48    | HCC               | LDLT        | FK                 | AML-M2a            | 27                 | CTx        | 11            | Dead   |
| 6           | M/54    | HBV LC            | Cadaveric   | FK+MMF             | HCC                | 42                 | TACE       | 17            | Dead   |
| 7           | M/36    | HBV LC            | LDLT        | FK+MMF             | HCC                | 23                 | RFA+RTx    | 10            | Dead   |
| 8           | M/48    | HCC               | Cadaveric   | FK                 | Pancreatic cancer  | 85                 | CTx        | 11            | Alive  |
| 9           | M/55    | HBV LC            | Cadaveric   | FK                 | Gastric cancer     | 73                 | OP+CTx     | 20            | Alive  |
| 10          | M/58    | Alcoholic LC      | Cadaveric   | FK+MMF             | Gastric cancer     | 40                 | OP         | 24            | Alive  |
| 11          | M/52    | HCC               | Cadaveric   | FK                 | Colon cancer       | 22                 | OP         | 24            | Alive  |
| 12          | M/49    | HBV LC            | Cadaveric   | FK                 | Renal cancer       | 84                 | OP         | 9             | Alive  |
| 13          | F/40    | HCC               | Cadaveric   | FK                 | Lung cancer        | 13                 | OP         | 40            | Alive  |
| 14          | M/52    | HCC               | Cadaveric   | FK                 | Nasopharyngeal cancer | 63           | RTx        | 32            |        |
| 15          | F/47    | HBV LC            | Cadaveric   | FK                 | Cervix cancer      | 85                 | CTx        | 10            | Dead   |
| 16          | F/49    | HBV LC            | Cadaveric   | FK                 | Cervix cancer      | 56                 | OP         | 37            | Alive  |
| 17          | F/50    | Cholelithiasis    | Cadaveric   | FK+MMF             | Adenocarcinoma in abdominal wall | 8         | None       | 6             | Dead   |

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; LC, liver cirrhosis; LDLT, living donor liver transplantation; FK, tacrolimus; MMF, mycophenolate mofetil; PTLD, post-transplant lymphoproliferative disorders; MDS-RAEB, Myelodysplastic syndromes-refractory anemia with excess blasts; AML, acute myeloid leukemia; CTx, chemotherapy; RTx, radiotherapy; OP, operation; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation.

*Time period from liver transplantation to de novo cancer; #Time period from the diagnosis of de novo cancer to last follow-up.

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study in USA reported the incidence was 13.7% in 534 recipients, which was significantly higher than that in matched population [9]. Results were similar in multicentric studies. Ettorre et al collected 1675 LTx recipients in six Italian transplantation centers and showed a total of 98 patients (5.9%) were diagnosed with de novo cancers after 5.2 years [10]. One cohort study in Australia using population-based liver (n = 1926) and cardiothoracic (n = 2718) registries showed the risk of any cancer in liver and cardiothoracic recipients was significantly elevated compared to the general population [17]. Another national wide study of the OPTN/UNOS database showed that in a cohort of 43,196 adult liver recipients 1,923 developed de novo malignancy representing an
It has been clear that the risk factor of de novo cancer is multifactorial. Recent studies have suggested that immunosuppression, age and other factors specific for different types of cancer were involved in the development of de novo cancers after LTx. First, the intensity of life-long immunosuppressive treatment could be the major reason for this serious complication [21]. Because exogenous immunosuppression is believed to suppress the host defense system including T cells, macrophages and natural killer cells, which normally provide surveillance and protection from oncogenic virus infection and even, destroy tumor cells [22]. Some studies have shown many immunosuppressive agents were related to a higher incidence of de novo cancer, for instance, azathioprine and cyclosporine to cutaneous neoplasia [23], tacrolimus to haematological malignancies [21]. Furthermore, patients receiving tacrolimus had a higher risk of neoplasia than those receiving cyclosporine [16,24]. On the other hand, withdrawal of immunosuppressive drug could result in regression of PTLD in many cases [21].

In our series, most patients received tacrolimus based therapy [25]. In our series, most patients received tacrolimus based therapy [25]. In our series, most patients received tacrolimus based therapy [25]. In our series, most patients received tacrolimus based therapy [25].

Given the role of immune system in tumor surveillance, evidence is accumulating that patients with premalignant conditions before LTx could have higher risk for developing cancers in

![Figure 2. The number of de novo cancer cases developed in the different follow-up years after liver transplantation.](https://www.plosone.org/article/figure/10.1371/journal.pone.0085651.g002)
the setting of immunosuppression, for example, the relationship between Barrett’s oesophagus and oesophageal cancer, colonic polyp and colon cancer, Budd-Chiari syndrome and acute leukemia [31]. It is also clear that patients underwent LTx for malignant liver diseases have a high risk of tumor recurrence. However, no evidence has been clarified whether malignant conditions before LTx could be a risk factor for developing de novo cancers after LTx. Our results indicated that the incidence rates were comparable between patients who had malignant liver diseases at time of transplant and those with benign diseases. This was in accordance with the observations form Herrero et al showing HCC was not a risk factor for the development of de novo cancer after LTx [16]. Indeed, some specific factors have been suggested for certain cancer types. For example, PTLD can be considered an opportunistic infectious complication usually involving the Epstein-Barr virus [32]. HCC is associated with hepatitis B virus (HBV) recurrence after LTx [33]. In our series, all the patients developed PTLD were detected Epstein-Barr virus positive after LTx, and the two patients with de novo HCC had HBV recurrence before developing HCC, thus supporting the previous findings.

From the previous studies, the most common de novo cancer after organ transplantation was skin cancer followed by PTLD in Western populations [13]. However, unlike Western countries, no skin cancer was diagnosed among our series. Similar finding was also reported in a study from Taiwan, which reviewed 560 renal transplant recipients for the pattern of cancer occurring after transplantation [34]. Another larger series report from a liver transplant center in Korea also noted that the incidence of skin cancer was relatively low among Korean LTx recipients (only 2 skin cancer in a total of 44 de novo cancers after LTx) [6]. The Japanese study also showed that colorectal cancer was the most commonly detected malignancy after living donor liver transplantation [20]. Moreover, the most common de novo cancers in our series were PTLD followed by lung cancer, gastric cancer and HCC. According to the common cancer incidence in Chinese general population, the top frequent cancers are lung cancer, gastric cancer, colorectal cancer and liver cancer [15]. The spectrum of cancers between LTx recipients and the general population was almost comparable. While based on our results, the relative risks of overall and individual de novo cancer were significantly higher in LTx recipients compared with in the Chinese general population (Table 3). Taken together, our results together with others, suggested that patterns of de novo cancer after organ transplantation might differ between Western and Eastern countries. Racial and social factors, including endemic environment could be the underlying explanation.

Recipients of organ transplantation are subjected to lifelong immunosuppression. Thus an increased incidence of developing cancer is expected in recipients with longer follow-up. The longer transplant recipients survive, the greater the risk of cancer accumulates. This was supported by the results in our series. We noted, as expected, that the number of de novo cancers increased as further follow-up accrued. Moreover, though receiving aggressive treatments after diagnosis, poor survival of those patients with de novo cancers was noted in our series. All the patients who died after the diagnosis had a direct relationship with the de novo cancers. Indeed, the causes of patient later death after LTx are multifactorial including chronic rejection, primary disease recurrence and others. Recent studies have currently considered de novo cancer as the second leading cause of death following cardiovascular complications [2,13]. It has been clear that tumor recurrence...
is the major cause of death after LTx for recipients of malignant liver disease [35]. However, after excluding the patients who died of tumor recurrence, our single center study showed that the survival of patients with de novo cancers was significantly lower than those without de novo cancers, suggesting that compared with non-tumor factors de novo cancer has contributed more to the later mortality after LTx in Chinese population.

Conclusion

Our findings suggested that liver transplant recipients were at increased risk for developing de novo cancers after LTx. The incidence rates and spectrum of de novo cancers in Chinese population were different from Western people due to racial and social factors. Gender and age might be the risk factors but pre-transplant malignant condition had no relationship to de novo cancer. However, further studies were still needed. The increased prevalence of de novo cancer during accrued patient survival was the main cause of patient later mortality after LTx.

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Author Contributions

Conceived and designed the experiments: SFY SSZ. Performed the experiments: SFY FG MZ. Analyzed the data: SY JY. Contributed reagents/materials/analysis tools: JY SY JW. Wrote the paper: SY FG. Contributed to the discussion: WLW SSZ.

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