Recurrent Nonhepatic and De Novo Malignancies After Liver Transplantation

Ashokkumar Jain,[1,2,4] Omer Fiaz,[3] Baber Sheikh,[2] Rajeev Sharma,[1] Saman Safadjou,[1] Randeep Kashyap,[1] Leah Bryan,[1] Pam Batzold,[1] and Mark Orloff[1]

Introduction. After Liver transplantation (LTx), recurrence of hepatic cancer, de novo cancers, and donor-transmitted cancers have been described. However, the data for patients with a prior history of nonhepatic malignancy and its recurrence post-LTx are limited.

Aim. Aim of this study was to examine the patient with nonhepatic pre-LTx malignancies, and their recurrence post-LTx along with de novo cancers and recurrence of hepatic malignancy in the population.

Patients and Method. Between March 1996 and July 2006, 1127 patients underwent LTx at our institution. Thirty patients (2.7%) (15 men and 15 women, mean age 56.9±12.8 years) had documented nonhepatic malignancies. There were seven colorectal, three prostatic, three cervical, three bladder, six breast, and other nine miscellaneous cancers (one patient had two cancers). Four patients had hepatocellular carcinoma at the time of LTx. All patients were followed up until 2008 with a mean follow-up period of 34.1±35.3 months.

Results. One patient with oropharyngeal cancer (3.3%), who was recurrence-free pre-LTx for 77.3 months, developed recurrence 36 months post-LTx and subsequently died 11 months postrecurrence. Two patients developed de novo cancer. One developed renal cell carcinoma 46.6 months post-LTx and other developed de novo intra-abdominal metastatic adenocarcinoma of unknown origin. Three of four patients developed recurrent hepatocellular carcinoma.

Conclusion. The rate of recurrence of nonhepatic malignancy was 3% and de novo cancer was 6% in the present series. There is a need to develop a guideline for recurrence-free survival period for nonhepatic malignancies before LTx, based on the type and stage of cancer.

Keywords: Liver transplantation, Malignancy, Immunosuppression, Hepatocellular carcinoma, Guidelines, de Novo cancers.

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The advances in transplantation medicine have led to improved outcome of liver transplantation (LTx), increasing age limits, and widening of indications. With better immunosuppressant and close follow-up (*1*), the long-term outcome after LTx has improved. Furthermore, the number of patients with a history of previous nonhepatic malignancy presenting to liver transplant units for LTx evaluation are growing. Late deaths and graft losses are not related to rejections but to age-related complications, recurrence of the disease, and de novo cancers (*2*). The rate of deaths from de novo cancers increases with longer follow-ups (*3–5*). Malignancy-related deaths are caused not only by de novo cancers but also by recurrence of hepatic malignancies and donor-transmitted malignancies (*6–9*).

Previously, these patients were selected or rejected on the basis of individual clinical decisions. In contrast to renal-transplant recipients, no distinct data could predict their outcome. There are several reports on de novo cancers, hepatic cancers, and donor-transmitted malignancies in postliver transplant recipients (*3*, *6–9*). However, data about recurrent cancers after LTx in patients with a history of successfully treated nonhepatic malignancy are limited (*10*).

Penn et al. (*11–13*) reported recurrence of nonhepatic malignancies posttransplantation. However, to evaluate the risk precisely, such data from registry do not provide the precise information about the details of recurrences post-LTx and the patient population at risk. In that respect, single-center data with long-term follow-up becomes more informative.

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[1] Department of Surgery, University of Rochester Medical Center, Rochester, NY.
[2] Department of Surgery, Temple University Hospital, Medical Office Building, Philadelphia, PA.
[3] Division of Medical Students, Vrije Universiteit Amsterdam, van der Boechorststraat 7, Amsterdam, The Netherlands.
[4] Address correspondence to: Ashokkumar Jain, M.D., F.A.C.S., Division of Abdominal Organ Transplantation, Department of Surgery, Temple University Hospital, 3322 N. Broad Street, Medical Office Building, Suite 147, Philadelphia, PA 19140.
E-mail: ashokkumar.jain@tuhs.temple.edu

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Aim

Aim of this study was to evaluate the patients who were successfully treated for nonhepatic malignancy pre-LTx and asses their recurrence-free survival outcome post-LTx along with any de novo malignancy or recurrent hepatic malignancy in the population. In addition, this study also aims to develop a guide line for recurrence-free survival period for nonhepatic malignancy before LTx based on nature and stage of malignancy.

PATIENTS AND METHODS

A retrospective review of 1127 patients who underwent LTx between March 1996 and July 2007 was performed, and 30 patients (2.7%) with pre-existing nonhepatic malignancy were identified. All 30 patients were treated for on-hepatic malignancies without any evidence of recurrence. Recurrence-free state was confirmed on clinical examination, CT-scans, and bone scans. Data were collected on patient demographics, associated diagnosis, and pre-LTx treatment (surgery, chemotherapy, or radiotherapy). In addition, data were collected on recurrence post-LTx by clinical examination, CT scans, and bone scans. Values are presented as mean± standard deviation.

The indications for liver transplant were Laennec's cirrhosis (n=10), hepatitis C-related cirrhosis (n=6), cryptogenic cirrhosis (n=5), primary sclerosing cholangitis (n=3), primary biliary cirrhosis (n=2), autoimmune hepatitis (n=2), hepatitis B viral infection-related cirrhosis (n=1), and nonalcoholic steatohepatitis (n=1). In addition, four patients had hepatocellular carcinoma (HCC) at the time of liver transplant.

RESULTS

Thirty patients were found to have 31 nonhepatic malignancies (one patient; case 30 had two separate nonhepatic malignancies). There were 15 male and 15 female patients with a mean age of 56.9±12.8 years. All patients were followed up until July 2008. Mean follow-up was 34.10±35.26 months post-LTx (Table 1).

Recurrence of Nonhepatic Malignancy

Recurrence of nonhepatic malignancy was observed in one patient (case 21). She had a pre-LTx history of squamous cell carcinoma of right retromolar trigone (pT3N1M0). She was managed with radical resection (laryngectomy with full-thickness rotational skin graft) and postoperative radiotherapy. A total of 77.3 months later, she developed end-stage liver disease. Because she remained recurrence-free, she underwent LTx. Thirty-six months post-LTx, she developed a recurrence of oropharyngeal cancer. She was managed with chemotherapy by the oncologist. She had oropharyngeal bleeding and died at home because of cardiorespiratory arrest 11 months postrecurrence and 47 months post-LTx.

De Novo Malignancies

One patient (case 6) had cervical carcinoma (managed with hysterectomy) 98.8 months before LTx. She developed de novo renal cell cancer 46.6 months post-LTx and presented with lung and brain metastases; she subsequently died 46.6 months post-LTx. However, there was no evidence of recurrence of original nonhepatic malignancy. Another patient (case 26) had breast cancer 37 years before transplant. She was successfully treated with radical mastectomy. She was presented with intra-abdominal metastatic disease of unknown primary 19 months post-LTx. Biopsy showed poorly differentiated adenocarcinoma with signet ring cells suggestive of intra-abdominal primary.

Recurrence of Hepatic Malignancies

Besides these three of four patients with HCC (Table 2), three died of recurrence from HCC at 39.6 months, 14.9 months, and 1 year post-LTx, respectively.

DISCUSSION

In the last 2 decades, because of the increase in post-LTx survival rate, an increasing number of centers are performing LTx. The patient referral and selection for LTx has widened. The number of patients with relatively high risk is being considered for LTx who might not have been considered suitable for LTx 10 to 20 years ago. In the last decade or 2, patients with increasing age (>65 years) or patient with previous ischemic heart disease or cerebrovascular accident have been offered LTx. Similarly, after careful selection, patients with previous nonhepatic malignancy with hepatic failure have been listed and transplanted. Although there are several citations on the recurrence of hepatic malignancy, de novo cancers and donor-transmitted cancers, there is little information in the literature on the history of nonhepatic malignancies before LTx (*10*, *11*, *13–16*).

In this series, we found 30 cases (2.7%) of nonhepatic malignancies that were recurrence free from 6 to 477 months pre-LTx, with a mean follow-up of 34.10±35.26 months. One patient (3.3%) had a recurrence of laryngeal cancer and died 47 months post-LTx from cardiorespiratory failure. She was recurrence free for 77 months pre-LTx.

It is interesting to note that of 30 cases, one patient had two nonhepatic malignancies and the other four patients had hepatic malignancies before LTx. Post-LTx, overall, one patient had recurrence of nonhepatic malignancy, two patients had de novo malignancies, and three patients had recurrence of hepatic malignancies. This accounts for 37 cancers in 30 patients (1.23 cancer sites/patient). Six patients died (20.0%), where the cause of death was directly related to malignancy. The patients with a history of nonhepatic malignancy may have a higher preponderance for de novo or recurrence of hepatic malignancy.

In this series, we did not have any hematologic malignancy. The recently published data by Benten et al. (*10*) described 37 patients, including 11 patients with (29.7%) with hematological malignancies. Three of them had acute disease at the time of LTx. In other series by Saigal et al. (*16*), of 18 cases of pre-existing nonhepatic malignancy, six cases (33.3%) had myeloproliferative disease.

In the study by Benten et al. (*10*), one patient (2.7%) had recurrent (rectal) cancer in a follow-up period of 4 to 131 months. This is comparable with our experience in rate of recurrence. However, Penn et al. (*11*, *13*) from registry data reported recurrence of nonhepatic malignancies post-LTx with a recurrence rate of 7% to 23%. Higher rates were observed for soft-tissue sarcomas, breast cancers, and symp-

TABLE 1. Basic clinical data for LTx recipients with a tumor history

S. No.	Age at transplant (yr)	Sex	Diagnosis	Pre-existing nonhepatic cancer	Type/size/stage	Therapy	Months to LTx	Months post-LTx
1	41.5	M	Hepatitis C	Skin	Melanoma	Excision	150.2	72.87
2	62.9	F	PBC	Rectal	T3 SCC	Excision, 5FU, RT	50	59.34
3	75	M	Laennec's, HCC	Prostate	Gleason score: 9	RT	39.6	9.29
4	52.2	M	PSC	Colon	Adenocarcinoma	Colectomy with ileostomy	75.4	87.62
5	72.2	F	Cryptogenic, HCC, ReTx: PNF	Skin	Melanoma	Excision	196.6	14.91
6	44.7	F	Hepatitis C	Cervical		Hysterectomy	98.8	46.6
7	14.2	F	Cryptogenic	RMS		CT and RT	33.7	87.32
8	66.3	M	Laennec's	Bladder	Transitional cell carcinoma	Multiple TURBT	254.7	52.58
9	48	M	PSC	Colon	Adenocarcinoma	Total colectomy, ileostomy, CT	115.7	11.36
10	65.8	F	NASH, ReTxp: PNF	Breast		Right mastectomy	70.8	92.22
11	69.7	M	Laennec's, HCC	Bladder	Transitional cell carcinoma	Surgery	74	76.98
12	58.6	F	PBC	Breast		Left mastectomy	247.5	4.24
13	62.8	F	Laennec's	Cervical		RT	300	139.24
14	56.1	M	Hepatitis C	Colon	Adenocarcinoma	Resection	78.4	48.64
15	65	M	Cryptogenic	Bladder	2.5 papillary tumor in the left bladder wall	Local excision	53.6	25.39
16	41.5	F	Laennec's	Melanoma		Resection	224.5	16.88
17	43.7	M	Hepatitis C	Renal	2.3 cm dimension	Nephrectomy	20.4	7.49
18	59	F	Laennec's	Breast		Lumpectomy, right breast and RT	114.9	12.18
19	61.6	M	Hepatitis C	Colon	Adenocarcinoma	Total colectomy, RT	370.3	17.57
20	55	M	Laennec's	Prostate		Radical prostatectomy	39.7	24.96
21	56.8	F	Laennec's	Oropharyngeal	T3N1M0	Surgical excision followed by RT	77.3	47
22	58	F	Autoimmune	Breast	1.5 cm, stage T1N0M0	Lumpectomy and RT	67.6	1.71
23	48.6	F	Laennec's	Ovarian	Papillary serous ca (2.8 cm), no stromal invasion.	Surgical excision, BSO & hysterectomy	95.6	19.77
24	70	M	Cryptogenic	Colon	Adenocarcinoma	Colon surgery	66	9.89
25	55.9	M	Hepatitis C, HCC	Prostate	Gleason score: 6*	Antiandrogen therapy, brachytherapy	17.3	1.08
26	72.4	F	Cryptogenic	Breast		Radical mastectomy	477.2	18.72
27	62	M	Hepatitis B	Pancreas	Islet cell	Distal pancreatectomy with splenectomy	6.1	9.79
28	72.4	F	Autoimmune	Cervical		Hysterectomy	449.5	0.43
29	44	M	PSC, ReTxp: HAT	Colon, skin		LAR followed by CT and RT	146.3	2.04
30	50.8	F	Laennec's	Breast/uterine		Lumpectomy, hysterectomy, CT, RT	111.3	4.99

Rec, recurrence; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; PNF, primary non-function; RMS, rhabdomyosarcoma; RCC, renal cell carcinoma; NASH, non-alcoholic steatohepatitis; HAT, hepatic artery thrombosis; LAR, low anterior resection; BSO, bilateral Salpingo-oophorectomy; *, adenocarcinoma of the prostate, stage T1cN0M0; CT, chemotherapy; RT, radiotherapy; ReTxp, retransplant; SCC, squamous cell carcinomam; LTx, liver transplantation.

TABLE 2. Patients with HCC

Case	Type of LTx	Pre LTx therapy	Radiological tumor size (cm)	Explant tumor size (cm)	Last follow-up
3	DDLT	None	2.2	2.2	Died 39.6 mo post-LTx from recurrent bone mets
5	DDLT[a]	None	(11 mo pre LTx), 3.2 (1 mo pre LTx), 6.0	5.5	Died 14.9 mo from adrenal metastatic disease
11	LDLT	Chemoembolization	(6 mo pre LTx), 2 (3 mo pre LTx), 5.5	3 Lesions; 3.7, 3.0, and 0.7	Alive 77 mo post-LTx
25	DDLT	None	3	3 Lesions; 3.7, 3.0, and 0.7	Died 1 yr post-LTx from metastatic cancer

[a] Received re-LTx for primary nonfunction.
HCC, hepatocellular carcinoma; LTx, liver transplant; DDLT, deceased donor liver transplant; LDLT, live donor liver transplant.

TABLE 3. Suggested guide lines of recurrence free waiting period for non hepatic malignancy and liver transplantation

1	Myeloproliferative disorder with Budd-Chiari	No contraindication to LTx	Saigal et al. (*16*), Benton et al. (*10*)
2	In situ cancers (kidney, colon)	Surgery before, during or after LTx waiting period not necessary	Saigal et al. (*16*), Penn et al. (*12*, *23*)
3	Most cancers early stages in most of cases	Recurrence free survival 2 to 5 yr before LTx	Penn et al. (*12*, *23*)
4	Lymphoma, carcinoma of the breast, prostate, colon, and large (>5 cm) symptomatic renal cell carcinoma	Recurrence free survival >5 yr	Penn et al. (*12*, *23*)

LTx, liver transplant.

tomatic renal-cell carcinomas. Lower rate was reported for uterine, testicular, thyroid, and cervical cancers. This incidence seems to be much higher than single-center reports. This disparity may be related to voluntary enrolment in the registry. Many patients with nonhepatic malignancies may not have been catalogued accurately. Thus, the population at risk could be much higher than projected. However, Kelly et al. (*15*) did report a recurrence rate of 13.8% in 29 cases of nonhepatic malignancy.

Currently, there is no existing guideline to show the duration of recurrence-free survival time for different types of cancers before it is safe for them to undergo LTx. Obviously, it would depend on the type, stage, and grade of the malignancy. More careful prospective collection of such data from all the transplant centers is necessary to derive any guidelines. However, with current practice, it does seem that most of the clinicians have exercised good judgment in selecting and transplanting such cases. Usually, a transplant team would evaluate such patients in great detail to rule out any clinical or radiological signs or symptoms of recurrence before LTx. Also, most centers would wait from 2 to 5 years for recurrence-free interval before subjecting a patient to LTx. Saigal et al. (*16*) and Benten et al. (*10*) successfully performed LTx in the presence of myeloproliferative disorders. Saigal et al. (*16*) suggested that pre-existing malignancy is not a contraindication for LTx, provided malignancy is amenable to curative therapy pre-LTx. Penn et al. (*12*) retrospectively examined 1297 cases of pre-existing malignancies in renal transplant patients (*12*). A recurrence rate of 21% was found in patients who were successfully treated before renal transplant. He suggested that a waiting period of 2 years was safe in most cases but 5 years was desirable for lymphomas, carcinomas of the breast, prostate, colon, and large (more than 5 cm) symptomatic renal-cell carcinoma. He also suggested that for small tumors and in situ lesions, waiting period is not necessary. Indeed, radical nephrectomy for renal-cell carcinoma at the time of LTx has been described by Fayek et al. (*17*) (two cases) and Saigal et al. (one case) independently. Saigal et al. (*16*) also reported four cases of incidental cancers diagnosed at the time of LTx. Three of these had successful outcome. Similarly, in cardiac transplant, 2 years of recurrence-free waiting period in most cases has resulted in 100% patient survival. Of seven patients described by Dillon et al. (*18*), only one patient had well-differentiated endometrial carcinoma. She underwent cardiac transplant 20 days posthysterectomy. Only one patient had recurrence of basal cell carcinoma of the skin. Other six patients were recurrence free in the follow-up period (mean 31 months).

It was surprising that in our series, recurrence occurred in the patient who had nearly 6 years of recurrence-free survival pre-LTx (and 3 years post-LTx), where most would have considered it as a safe period for transplantation. It is possible that with immunosuppressive agents one could never rule out such possibilities of recurrences because of impaired host surveillance for cancer cells (*19–22*). However, with currently available limited knowledge, all one could say is that myeloproliferative disorders with Budd Chiari are not a contraindication to LTx (*10*, *16*). For carcinoma in situ, no waiting period is necessary and surgery can be performed before, during, or after LTx (*13*, *16*, *23*).

Certainly, we do not know how many cases of nonhepatic malignancies were not considered for LTx. Then, the

question would arise whether we are too conservative in transplanting such cases? However, in future with the increasing amount of transplant centers, and the increasing rates of referral, some form of guideline from the proposed data would be helpful. After reviewing the literature on the recurrence of nonhepatic malignancies in LTx and other solid organ transplantation, we have summarized a preliminary guide line in Table 3. However, a multicenter approach with long-term prospective follow-up of the patients is required to establish a firm guideline. Also, the prospect of this group of patients at higher risk of developing other type of hepatic or nonhepatic cancer before or after LTx would need further careful consideration.

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