Evolution and management of de novo neoplasm post-liver transplantation: a 20-year experience from a single European centre

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Abstract

Purpose Survival post-liver transplantation (LT) has improved; however, patients are considered at the risk of malignancy due to prolonged immunosuppression. The long-term outcome of patients developing de novo neoplasm (DN) at our centre was evaluated.

Methods Between October 1988 and December 2007, 800 LT were performed in 742 patients. Patients were divided into two study periods according to the time of LT; first: October 1988–December 1995; second: January 1996–December 2007.

Results After a mean follow-up of 5 ± 4.6 years, 71 DN (9.5%) were detected in 742 patients. The cumulative risk of DN development increased with the time from LT although no differences at 3, 5, and 10 years were found when first and second periods were compared (3, 7, 16% vs. 2, 4, 11%, respectively; $p = 0.4$). DN incidence was higher in the first compared with the second period (10.7 vs. 7.8%; $p < 0.04$); no significant differences were observed in mortality rate (50 vs. 27%; $p = 0.052$). Actuarial patient survival post-DN at 1, 3, and 5 years: 67, 48, 45% versus 82, 71, 65%, in the first versus second period, respectively, $p < 0.04$.

Conclusions DN incidence has decreased in recent years; however, as survival post-LT increases, so does the incidence of DN. Surveillance programmes are necessary to diagnose DN at early stages.

Keywords De novo neoplasms · Immunosuppression · Surveillance · Survival

Introduction

The number of successful liver transplants performed in the last two decades has increased owing to multiple factors, such as the advent of new immunosuppressive agents, and amelioration in pre- and post-transplant management, among others. Patient survival currently stands at 90% at 1 year and 70% at 5 years [1].

However, liver transplantation (LT) recipients are considered to be at increased risk of malignancy because of prolonged immunosuppression therapy [2]. In different studies [3–5], de novo neoplasm (DN) has been described as a leading cause of late mortality after LT, in up to 20% of cases. Our group recently reported that DN represented the third cause of late mortality post-LT [6]. The development of DN has been ascribed to a multifactorial combination of individual and regional predispositions to malignancy, pre-transplantation disease states, recipient viral status, and the use of different immunosuppression regimens [7].

The risk of DN development has been reported to increase with the time elapsed from transplantation [8]. In order to assess the evolution of DN in our LT programme, we retrospectively analyzed a 20-year period of our own experience.

Thus, the aim of this study was to ascertain the long-term outcome of patients who developed DN after LT at our centre.

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Materials and methods

Between October 1988 and December 2007, a total of 800 LT were performed in 742 patients at our hospital.

Study design

In order to analyze the evolution of DN, patients who had undergone LT were divided into two study periods according to the time of LT. The first period included patients transplanted between October 1988 and December 1995, and the second period patients between January 1996 and December 2007. Follow-up was performed until June 2009.

Immunosuppression

Immunosuppression regimens changed during the study period. From 1988 to 1994, immunosuppression was maintained by cyclosporine A (CyA) and prednisone (P). Induction therapy consisted of 1 g of methylprednisolone i.v. prior to revascularization, followed by P 200 mg/day, tapering to 20 mg/day over 6 days. CyA was started in the postoperative period at 2 mg/kg/day by continuous intravenous infusion, with the dose being increased to a steady-state level of 300–350 ng/ml determined by enzyme immunoassay during the first week. Oral CyA (10 mg/kg/twice daily) was begun with i.v. overlap to achieve a trough level around 100–150 ng/l by the end of the third month. Azathioprine was administered after the first week at 1–2 mg/kg/day. After the first month, P was progressively reduced until withdrawn between the third and sixth months post-transplant.

From 1994 to 1995, immunosuppression was maintained by cyclosporine neoral (CS) and P. Corticosteroids were administered as in the previous period. Oral CS was started in the operating room by nasogastric tube until oral intake was tolerated at 10–15 mg/kg/day (divided into two doses) to achieve a trough level around 200–400 ng/ml during the first month, 150–300 ng/ml during the second, and 100–200 ng/ml from the third month. After the first month, P was progressively reduced until withdrawn during the third month after transplant.

From 1995 to 2009, immunosuppression was maintained by tacrolimus (Tac) and P. Induction therapy consisted of 500 mg of methylprednisolone i.v. prior to revascularization, followed by P 200 mg/day, tapering to 20 mg/day over 6 days. Oral Tac was begun in the operating room by nasogastric tube until oral intake was tolerated at 0.05 mg/kg/twice daily to achieve trough levels around 10–15 ng/ml during the first month and 8–12 ng/ml at the end of the third month. After the first month, P was progressively reduced until withdrawn during the third month after transplant.

From 2000, immunosuppression in patients with hepatitis C virus (HCV) was maintained by Tac and mycophenolate-mofetil (MMF) without steroids. Tac + P were administered as in patients without HCV. Oral MMF was added to the immunosuppressive regimen as soon as possible at 1–2 g/daily. In patients with leucopenia, the initial dosage was 500 mg/twice daily. MMF was discontinued over the third month, if possible.

Renal insufficiency

Pre-transplant renal insufficiency

From 2000, immunosuppression in patients with pre-transplant renal insufficiency was usually maintained with a sequential quadruple therapy. Induction consisted of 500 mg methylprednisolone i.v. prior to revascularization, followed by P 200 mg/day, tapering to 20 mg/day over 6 days. Basiliximab (20 mg i.v.) was administered at the end of surgery and the same dose was repeated at day 4 post-LT. Oral MMF was started as soon as possible at 1–2 g/daily. Calcineurin inhibitors (CNI) were begun at half dosage or added to the immunosuppressive regimen once serum creatinine had improved. CNI were started in the first week in all patients.

Post-transplant renal insufficiency

In patients developing renal insufficiency during follow-up, CNI were reduced to the minimum dose and MMF or mTOR was added to the immunosuppressive regimen.

Acute rejection

Proven acute rejection episodes were treated with one to three bolus injections of 1 g methylprednisolone. Between 1988 and 1995, if rejection persisted, a 14-day course of OKT3 5 mg/day was given. P was gradually tapered and discontinued. Thereafter, if rejection persisted, one or two 3-day courses of steroid boluses were administered. In cortico-resistant cases, MMF 1 g/12 h (if the patient was not already being treated with MMF) was added to the treatment. If there was no response, rapamycin or everolimus was started at 5 mg/daily or 1 mg/12 h, respectively, to achieve trough levels of rapamycin and everolimus of 5–10 ng/ml and 3–8 ng/ml, respectively.

Infections

All viral, bacterial or fungal infections occurring after LT, during hospital stay or necessitating patient hospitalization were recorded. Blood cultures were performed to identify the origin of the infection in all cases.

Pre- and post-transplant cancer surveillance

Pre-LT evaluation protocols at our centre include abdominal CT, upper gastrointestinal endoscopy (to detect esophageal varices) and dermatological, gynecological, and urological examination. An extension study including brain and chest CT and bone scintigraphy is always performed in patients with hepatocellular carcinoma.

Patients are currently followed up at the outpatient clinic every 2 weeks during the first 2 months post-LT, once a month for the next 6 months and three times a year thereafter. A general examination is performed at each visit to identify suspicious clinical signs or symptoms of DN. Urological examination (including PSA measurement) is also performed in male patients over the age of 50 years.

De novo neoplasm

DN was defined as tumors that appeared, for the first time, after LT. In some of these patients, metachronous lesions of different origin developed; each lesion was counted as a different DN.

Owing to the different behaviour and heterogeneity of DN, a separate analysis was made between skin tumors and non-skin tumors. Regardless of the time of DN diagnosis, patients were assigned to a study period depending on the date of the first LT. The time to DN development was calculated from the date of the first LT (some patients received more than one graft) to the time of diagnosis of the patient's malignancy.

Survival after DN diagnosis was defined as a period from DN diagnosis to death or censored in June 2009.

Treatment of “de novo” neoplasm

Treatment of DN was based on the guidelines for tumors in non-immunosuppressed patients. Surgical treatment was offered to all patients who had resectable tumors with no disease spread at the time of diagnosis. Neoadjuvant and adjuvant treatment were based on tumor guidelines. Palliative treatment was offered when patients were diagnosed at advanced stages.

Immunosuppression was reduced to a minimum. Since 2006, our policy has been to reduce immunosuppression to a minimum and add mTOR inhibitors to the immunosuppressive regimen.

Statistical analysis

Comparisons between groups were made using the Mann–Whitney *U* test for continuous variables and the Chi-square test for categorical variables. Results are expressed as mean $\pm$ standard deviation and median (range). Estimation

of survival was made by Kaplan–Meier curves and compared using the log-rank test. $P < 0.05$ was considered statistically significant. All statistical analyses were made with SPSS 15.0 (SPSS Inc., Chicago, IL, USA.)

All data were prospectively collected and retrospectively analyzed from our database.

Results

After a mean follow-up of 5 ± 4.6 years, 71 DN (9.5%) were detected in 742 patients (Table 1).

No significant differences were found between both periods in acute rejection episodes, infection episodes and cortico-resistant rejection (Table 2).

The cumulative risk of DN development increased with the time from LT although no differences were found at 3, 5, and 10 years when the first and second periods were

Table 1 Tumor characteristics

Number of tumors	71
Skin Carcinoma	25 (35%)
Basal cell skin cancer	14 (56%)
Non-basal skin cancer	11 (44%)
Lung cancer	9 (13%)
Epidermoid carcinoma	8 (88%)
Adenocarcinoma	1 (12%)
Urological cancer	8 (11%)
Transitional cell bladder carcinoma	4 (50%)
Renal adenocarcinoma	2 (25%)
Prostate adenocarcinoma	2 (25%)
Colorectal cancer	6 (8%)
Colon adenocarcinoma	5 (83%)
Epidermoid anal carcinoma	1 (17%)
Gastro-oesophageal cancer	6 (8%)
Oesophageal epidermoid carcinoma	3 (50%)
Gastric adenocarcinoma	2 (33%)
Gastric GIST	1 (17%)
Oropharyngeal cancer	5 (7%)
Epidermoid laryngeal carcinoma	3 (60%)
Others	2 (40%)
Lymphoproliferative disorders	4 (6%)
Lymphoma	3 (75%)
Kaposi's sarcoma	1 (25%)
Epidermoid cervix carcinoma	2 (3%)
Breast adenocarcinoma	2 (3%)
Pancreas adenocarcinoma	2 (3%)
De novo hepatocellular carcinoma	1 (1.5%)
Lower extremity glomus tumor	1 (1.5%)

Table 2 Immunosuppression characteristics, rejection, and infection episodes

	1st period 1988–1995	2nd period 1996–2007	<i>p</i>
Number of patients	191	551	
Immunosuppression			
Tac + P	16%	84%	<0.001
Cyclosporine + P	77%	23%	<0.001
OKT3 administration	2.4%	0.2%	0.2
mTOR administration	2.4%	12.2%	<0.001
Acute rejection episodes	28%	25%	0.1
Infection episodes	65%	41%	0.1
Steroid bolus administration	9.5%	12%	0.3
Cortico-resistant rejection episodes	16%	24.5%	0.1

Fig. 1 Cumulative risk of DN development

compared (3, 7, 16% vs. 2, 4, 11%, respectively, $p = 0.4$) (Fig. 1).

Patient, DN, and transplantation characteristics

Patient, DN, and transplantation characteristics are shown in Table 3. No differences were found between patients and transplantation characteristics in the two study periods regarding age, sex, alcohol intake, smoking, CMV status, HCV+, and blood transfusion, except in immunosuppression and infection episodes. None of the patients with DN

Table 3 Characteristics of de novo neoplasms ($n = 71$)

Patient and transplantation characteristics	1st period 1988–1995	2nd period 1996–2007	<i>p</i>
Number of tumors	30/280	41/520	
Mean age (years)	58 ± 5	60 ± 9	0.6
Sex (M/F)	64%/36%	66%/34%	0.9
Drinker or ex-drinker	67%	58%	0.5
Smoker or ex-smoker	49%	61%	0.3
Donor CMV+	90%	73%	0.1
Recipient CMV+	86%	87%	0.9
VHC+	52%	58%	0.6
Operative blood transfusion (IU)	11 ± 17	5 ± 3	0.09
Immunosuppression			
Tac + P	27%	73%	<0.001
Cyclosporine + P	95%	5%	<0.001
Acute rejection episodes	42%	29%	0.2
Cortico-resistant episodes	9.1%	7.9%	0.1
Infection episodes	70%	45%	0.03
Steroid bolus administration	42%	25%	0.1
DN characteristics			
DN incidence	10.7%	7.8%	0.03
Age at DN diagnosis (years)	63 ± 7	63 ± 9	0.7
Time to diagnosis of DN (years)	5.3 ± 3.3	4.2 ± 2.4	0.1
Tumor characteristics			
Skin cancer	39%	34%	0.7
Solid cancer	52%	66%	0.2
Haematological cancer	9%	–	0.09
DN treatment	97%	95%	0.6
Surgery	42%	55%	0.3
Surgery + radiotherapy	12%	11%	0.8
Chemotherapy	15%	3%	0.06
Radiotherapy + chemotherapy	6%	11%	0.5
Immunosuppression			
Immunosuppression modification	10%	16%	0.5
Use of mTOR	3%	11%	0.3
Mortality and survival			
Mortality	26/30 (70%)	11/41 (30%)	<0.001
Mortality due to DN	50%	27%	0.05
Mortality due to other causes	50%	73%	0.09
Patient survival after DN diagnosis (years)	4.2 ± 4.5	2.8 ± 1.8	0.08
Mean follow-up (years)	6.3 ± 6.5	4.5 ± 3.4	<0.001

were treated with OKT3 in neither of the study periods. The incidence of DN was higher in the first period compared with the second (10.7 vs. 7.8%, $p < 0.04$) and the mortality rate due to DN that was higher in the first period.

Survival

Overall survival

One, 5- and 10-year patient survival in the first and second period was 66, 46, 36% and 81, 68, 56%, respectively ($p < 0.001$). Moreover, actuarial patient survival excluding those who developed DN was also higher in the second period compared with the first (79, 70, 56% vs. 61, 45, 36%, respectively, $p < 0.001$).

DN survival

Actuarial patient survival after DN at 1, 5, and 10 years was 75, 55, and 26%, respectively. When patients of both periods were compared, significantly better survival at 1, 3, and 5 years was observed in the second period when all causes of mortality were analyzed (67, 48, 45% vs. 82, 71, 65%, respectively; $p < 0.04$) (Fig. 2).

One, 3- and 5-year survival after DN was compared between patients with skin and non-skin tumors, with a higher survival rate being observed in patients with skin DN: 96, 96, 84% vs. 63, 39, 39%, respectively ($p < 0.001$). Differences in survival between skin cancer and other tumors are shown in Fig. 3.

Skin tumor group

No statistical differences were found in skin cancer incidence when the first period was compared with the second

(4.2 vs. 2.8%, $p = 0.1$). No differences between the study periods were observed regarding age, sex, alcohol intake, smoking, CMV status, HCV+, and blood transfusion, except in immunosuppression, acute rejection, bolus administration, and infection episodes (Table 4).

All skin tumors were surgically resected and mTOR inhibitors were not used in this group of patients. No mortality due to skin cancer was observed in our population.

Non-skin tumors

Characteristics of the non-skin tumor group are shown in Table 5. No differences were observed between the study periods regarding age, sex, alcohol intake, smoking, CMV status, HCV+, and blood transfusion, except in immunosuppression. No statistical differences were found in the incidence of non-skin cancer between the first and second periods (7.4 vs. 5.1%, $p = 0.1$). However, time from transplant to DN diagnosis was longer in the first period. Most DN could be treated when diagnosed and different treatments were applied. Mortality due to DN was higher in the first period compared with the second (Table 5).

Tumor recurrence

Tumor recurrence was observed in eight patients (17%): Four were systemic recurrences and four local recurrences. Tumor recurrence was 24% in the first period versus 12% in the second ($p = 0.2$).

Survival

Actuarial survival after non-skin DN at 1, 5, and 10 years in the first and second periods was 95, 67, and 29% versus 100, 75, and 47%, respectively, ($p = 0.3$).

Fig. 2 Actuarial patient survival according to study period

Fig. 3 Survival after DN according to type of tumor

Table 4 Characteristics of non-skin tumor group ($n = 46$)

Patient and transplantation characteristics	1st period 1988–1995	2nd period 1996–2007	<i>p</i>
Number of tumors	20/268	26/507	
Age at time of LT (years)	58 ± 6	59 ± 10	0.7
Sex (M/F)	71%/29%	64%/36%	0.6
Drinker or ex-drinker	76%	64%	0.4
Smoker or ex-smoker	57%	71%	0.3
Donor CMV+	93%	71%	0.1
Recipient CMV+	79%	84%	0.7
VHC+	43%	44%	0.9
Operative blood transfusion (IU)	6.6 ± 4	5.5 ± 3	0.3
Induction immunosuppression after LT			
Tac + P	29%	100%	<0.001
Cyclosporine + P	71%	–	<0.001
Acute rejection episodes	33.3%	32%	0.9
Infection episodes	62%	48%	0.4
Steroid bolus administration	23.5%	26%	0.8
DN characteristics			
DN incidence	7.4%	5.1%	0.1
Age at DN diagnosis (years)	63 ± 8	63 ± 10	0.9
Time to DN diagnosis (years)	5.8 ± 3.4	3.8 ± 2.3	0.02
DN treatment	95%	92%	0.7
Surgery	19%	36%	0.2
Surgery + radiotherapy	9.5%	12%	0.8
Chemotherapy	24%	4%	0.07
Radiotherapy + chemotherapy	9.5%	16%	0.5
Immunosuppression			
Immunosuppression modification	14.3%	16%	0.9
Use of mTOR	4.8%	16%	0.2
Mortality and survival			
Mortality	69%	31%	<0.001
Mortality due to DN	71%	29%	<0.001
Mortality due to other causes	19%	71%	<0.001
Median survival after DN diagnosis (months)	21 ± 24	27 ± 22	0.3

Discussion

The improvement in immunosuppression and better management of transplanted patients has led to a marked increase in post-LT survival. However, two main pitfalls exist: recurrence of HCV and the long-term side effects of immunosuppression. In this setting, malignancies represent a serious complication after organ transplantation, being a major cause of long-term mortality [3–5]. After 20 years of experience in LT, we were interested in analyzing the development and management of DN and how they have changed over the years.

Table 5 Characteristics of skin tumor group ($n = 25$)

Patient and transplantation characteristics	1st period 1988–1995	2nd period 1996–2007	<i>p</i>
Number of tumors	11/259	14/495	
Age at time of LT (years)	59 ± 5	60 ± 9	0.6
Sex (M/F)	50%/50%	69%/31%	0.3
Drinker or ex-drinker	50%	46%	0.8
Smoker or ex-smoker	33%	42%	0.7
Donor CMV+	83.3%	75%	0.7
Recipient CMV+	100%	92.3%	0.4
VHC+	67%	85%	0.3
Operative blood transfusion (IU)	18 ± 27	5 ± 2	0.1
Induction immunosuppression after LT			
Tac + P	18%	100%	<0.001
Cyclosporine + P	82%	–	<0.001
Acute rejection episodes	75%	25%	0.009
Infection episodes	83%	39%	0.04
Steroid bolus administration	73%	27%	0.03
DN characteristics			
DN incidence	4.2%	2.8%	0.1
Age at DN diagnosis (years)	63 ± 5	65 ± 8	0.5
Time to DN diagnosis (years)	4.3 ± 2.9	4.8 ± 2.6	0.7

The development of DN after LT has been described by some transplant groups [4, 7–9]. The first studies reported an incidence of 3–5% [10–12]; however, this has appeared to be higher, up to 22% [7]. In our experience, the incidence of DN post-LT was 9.5%, higher than the tumor incidence described in the general population by age groups [13], but similar to that reported in previous studies on LT recipients [14–17].

The incidence of DN in the first period of the study was found to be higher than in the second, probably due to the different immunosuppression management in the second period. In recent years, we have attempted to keep immunosuppression to a minimum, while in the early years of our transplant programme we may have been more aggressive with the anti-rejection therapy. In fact, there were more episodes of acute rejection in the first time period, and consequently more steroid bolus was administered. The direct link between aggressive immunosuppression and increased incidence of infective complication and post-transplantation lymphoproliferative disease (PTLD) in the first period can explain the over immunosuppression as possible cause of increased incidence of DN.

As recently published, close surveillance of DN promotes early diagnosis [8]. Our group has certainly become aware of DN over the years; thus, even though the incidence of DN was higher in the first period, when non-skin

tumors were analyzed, we found the time for diagnosis to be much shorter in the second period, probably due to this better surveillance. Moreover, we believe, this fact has led us to diagnose DN in advanced stages in the first period and, thus, both mortality and tumor-related mortality were more significant in that period of the study.

The increased incidence of DN post-LT is thought to be due to the depression of the immune system, viral and opportunistic infections, genetic predisposition, and possibly immunosuppression itself [18]. The most important triggering factor for DN development is probably long-term exposure to immunosuppressant agents [19]. We observed that as survival after LT increased, so did the cumulative risk of developing DN, which supports this theory.

Fortunately, the most frequent DN in our series were skin tumors, the most common DN described by other LT groups [2, 20–22]. The incidence of skin tumors differs in the different series, with an incidence ranging from 6.3% [2] to 70% [21]. In our series, skin tumors represented 35% of all DN, with an incidence of 3%. Differences in latitude and sun exposure and immunosuppressive protocols may explain these differences. We found no mortality in these patients, thus confirming the low mortality observed by other authors [9, 17, 23, 24]. In our outpatient clinic, dermatological evaluations are made in all patients so that these lesions can be diagnosed and treated. This must be a general recommendation to all groups when transplanted patients with long-term follow-up are evaluated since skin tumors represent the most frequent DN and can be easily treated and cured.

Lung tumors constituted the most common non-skin tumor post-LT in our population, with a frequency of 13%. Most of these tumors were detected in advanced stages, thus implying poor survival. Early detection is essential for a favourable outcome, since only patients diagnosed at an early stage can be successfully treated. It has recently been suggested that transplanted patients may benefit from chest CT screening for early detection [8].

Colorectal cancer has been related to LT for primary sclerosing cholangitis (PSC) and concomitant ulcerative colitis [25–27]. In our study, the rate of colorectal cancer was low, 8%, and none of the patients were transplanted because of PSC. In a recent study by Filkenstedt et al. [8], only one patient with colorectal cancer had a history of PSC; thus, colorectal cancer, like other cancers, may be influenced by immunosuppression.

The incidence of lymphomas and PTLN has been reported to be increased in immunosuppressed patients with EBV [28]. We found a low incidence of lymphomas and without PTLN, and all the cases occurred in the first period of the study. Probably, patients in the second period had better immunosuppression control.

In the general non-transplanted population, advanced age usually carries an increased risk for specific tumor development; however, the transplanted population developing DN is younger than the general population [19].

More than half of the patients with non-skin tumors died during follow-up as a result of their tumors. Mortality was higher in the first period, although no differences were observed in the mean survival of patients in the two periods, and patients survived for approximately 2 years once the tumor had been diagnosed. This was probably due to the fact that follow-up was longer in patients in the first period. On the other hand, patients diagnosed of DN in recent years may have been treated more aggressively and immunosuppression management has changed, as described previously. As confirmed by our data and by other groups [29, 30], mortality due to DN is clinically significant and when patients develop DN, their survival is impaired.

DN must be treated aggressively in the same way and following the same guidelines as tumors occurring in non-immunosuppressed patients. If chemotherapy or radiotherapy is indicated, they must be applied at standard doses since the risk of graft loss is minimum. In our series, graft loss after these treatments was not observed. Patients who receive surgical treatment for DN have better survival; thus, in our opinion, we must be surgically aggressive whenever possible. When survival after DN was analyzed, we found 5-year survival of 55%, which is probably higher than that described by other groups [15, 31] and may be due to the high percentage of patients developing skin tumors with nil mortality. In fact, when survival was compared between patients with skin and non-skin tumors, differences were evident. It has been well described that patients who develop DN have shorter survival post-LT [23] and that the DN represents a major cause of late mortality following DN, as recently published by our group [6]. Although a case-control analysis to assess this fact was not made in the present study, shorter survival after DN was observed in patients developing non-skin tumors.

Immunosuppressed patients develop more aggressive tumors, which become difficult to treat. Although patients with DN have a better survival in the second period of study, we must take into account that the overall patient survival was also better in this period. However, other facts should be considered in order to explain this result. We have become more concerned about DN in recent years, and so patients have been diagnosed in earlier stages of their disease and thus the treatments were more effective. In fact, curative treatments could have been applied in more patients in the second period. On the other hand, most of the patients that developed DN in the first period were immunosuppressed with CyA as the main

immunosuppressant. In a study conducted in kidney transplant patients from OPTN/UNOS including more than 50,000 patients, the authors showed that patients immunosuppressed with CyA had a significant higher incidence of DN compared to those treated with Tac [32]. Therefore, CyA-based regimens could have a negative influence in the development of malignancy in the transplant population.

Another important factor that may have contributed to better survival in the second period was immunosuppression management once DN was detected. As described in several studies [33–35], mTOR inhibitors reduce the development and recurrence of DN and may be used in the complicated treatment of DN [36]. Moreover, a reduction in immunosuppression has also been reported to contribute to the management of DN. Patients in the second period had a more aggressive reduction in immunosuppression and mTOR inhibitors were used in a higher number of patients. Based on the literature [37], mTOR inhibitors should form part of the immunosuppression regimen in patients who develop DN, and in our department patients with DN are converted to mTOR inhibitors as soon as possible. The results of this strategy, together with the efficacy of mTOR after LT in preventing DN, should be evaluated in the near future.

In summary, after a 20-year experience in LT we found that the incidence of DN had decreased in recent years. On the other hand, as patient survival after liver transplantation increases, so does the incidence of DN. As most DN are aggressive tumors with a low survival rate after being diagnosed, surveillance programmes for DN detection are necessary and will help us to diagnose DN at early stages and be able to treat our patients accordingly.

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References

1. Registro Español de Trasplante Hepático (RETH). Memoria 1984–2006. <http://www.ont.es/RETH>
2. Penn I. The problem of cancer in organ transplant recipients: an overview. *Transplant Sci* 1994;4:23–32
3. Rabkin JM, De la Melena V, Orloff SL, Corless CL, Rosen HR, Olyaei AJ. Late mortality after orthotopic liver transplantation. *Am J Surg* 2001;181:475–479
4. Sheiner PA, Magliocca JF, Bodian CA, Kim-Schluger L, Altaca G, Guarrera SV, Emre S, Fishbein TM, Guy SR, Schwartz ME, Miller CM. Long-term medical complications in patients surviving >5 years after liver transplant. *Transplantation* 2000;69:781–789
5. Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, Abu-Elmagd K, Marsh W, Madariaga J, Mazariegos G, Geller D, Bonham CA, Gayowski T, Cacciarelli T, Fontes P, Starzl TE, Fung JJ. Long-term survival after liver transplantation in 4000 consecutive patients at a single center. *Ann Surg* 2000;232:490–500
6. Dopazo C, Bilbao I, Escartín A, Lázaro JL, Sapisochin G. Risk factors of late mortality following liver transplantation. In Knudsen K. H, editors. *Liver Transplantation: Rejection, Therapy and Post-operative Complications*; 2008
7. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. *Crit Rev Oncol Hematol* 2005;56:87–99
8. Finkenstedt A, Graziadei IW, Oberaigner W, Hilbe W, Nachbaur K, Mark W, Margreiter R, Vogel W. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplantation. *Am J Transplant* 2009;10:2355–2361
9. Sanchez EQ, Marubashi S, Jung G, Levy MF, Goldstein RM, Molmenti EP, Fasola CG, Gonwa TA, Jennings LW, Brooks BK, Klintmalm GB. De novo tumors after liver transplantation: a single-institution experience. *Liver Transpl* 2002;8:285–291
10. Penn I. The changing pattern of posttransplant malignancies. *Transplant Proc* 1991;23:1101–1103
11. Jonas S, Reyes N, Neumann U, Neuhaus R, Bechstein WO, Guckelberger O, Tullius SG, Serke S, Neuhaus P. De novo malignancies after liver transplantation using tacrolimus-based protocols or cyclosporine-based quadruple immunosuppression with an interleukin-2 receptor antibody or antithymocyte globulin. *Cancer* 1997;80:1141–1150
12. Frezza EE, Fung JJ, van Thiel DH. Non-lymphoid cancer after liver transplantation. *Hepatogastroenterology* 1997;44:1172–1181
13. Instituto Nacional de Estadística. Encuesta de morbilidad hospitalaria. 1999. <http://www.ine.es>
14. Valero JM, Rubio E, Moreno JM, Pons F, Sanchez-Turrión V, Cuervas-Mons V. De novo malignancies in liver transplantation. *Transplant Proc* 2003;35:709–711
15. Benlloch S, Berenguer M, Prieto M, Moreno R, San Juan F, Rayón M, Mir J, Segura A, Berenguer J. De novo internal neoplasms after liver transplantation: Increased risk and aggressive behavior in recent years? *Am J Transplant* 2004;4:596–604
16. Levy M, Backman L, Husberg B, Goldstein R, McMillan R, Gibbs J. De novo malignancy following liver transplantation: a single-center study. *Transplant Proc* 1993;25:1397–1399
17. Haagsma EB, Hegens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaaker IJ, Slooff MJ, Jansen PL. Increased cancer risk after liver transplantation: a population-based study. *J Hepatol* 2001;34:84–91
18. Penn I. Posttransplant malignancies. *Transplant Proc* 1999;31:1260–1261
19. Penn I. Cancers complicating organ transplantation. *N Engl J Med* 1990;323:1767–1769
20. Saigal S, Norris S, Muiesan P, Rela M, Heaton N, O'Grady J. Evidence of differential risk for posttransplantation malignancy based on pretransplantation cause in patients undergoing liver transplantation. *Liver Transpl* 2002;8:482–487
21. Xiol X, Guardiola J, Menéndez S. Risk factors for development of de novo neoplasia after liver transplantation. *Liver Transpl* 2001;7:971–975
22. Mithoefer AB, Supran S, Freeman RB. Risk factors associated with the development of skin cancer after liver transplantation. *Liver Transpl* 2002;8:939–944
23. Herrero JJ, Lorenzo M, Quiroga J, Sangro B, Pardo F, Rotellar F, Alvarez-Cienfuegos J, Prieto J. De novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. *Liver Transpl* 2005;11:89–97
24. Jain AB, Yee LD, Nalesnik MA, Youk A, Marsh G, Reyes J, Zak M, Rakela J, Irish W, Fung JJ. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. *Transplantation* 1998;66:1193–1200

25. Oo YH, Gunson BK, Lancashire RJ, Cheng KK, Neuberger JM. Incidence of cancers following orthotopic liver transplantation in a single center: comparison with national cancer incidence rates for England and Wales. *Transplantation* 2005;80:759–764
26. Higashi H, Yanaga K, Marsh JW, Tzakis A, Kakizoe S, Starzl TE. Development of colon cancer after liver transplantation for primary sclerosing cholangitis associated with ulcerative colitis. *Hepatology* 1990;11:477–480
27. Knechtle SJ, D'Alessandro AM, Harms BA, Pirsch JD, Belzer FO, Kalayoglu M. Relationships between sclerosing cholangitis, inflammatory bowel disease, and cancer in patients undergoing liver transplantation. *Surgery* 1995;118:615–620
28. Lewin KJ. Post-transplant lymphoproliferative disorders. *Pathol Oncol Res* 1997;3:177–182
29. Aberg F, Pukkala E, Hockerstedt K, Sankila R, Isoniemi H. Risk of malignant neoplasms after liver transplantation: a population based study. *Liver Transpl* 2008;14:1428–436
30. Jiang Y, Villeneuve PJ, Fenton SS, Schaubel DE, Lilly L, Mao Y. Liver transplantation and subsequent risk of cancer: findings from a Canadian cohort study. *Liver Transpl* 2008;14:1588–9157
31. Catalina MV, de Diego A, Garcia-Sánchez A, Escudero M, Salcedo M, Bañares R, Clemente G. Characterization of de novo malignancies in liver transplantation. *Gastroenterol Hepatol* 2003;26:57–63
32. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Post-transplant de novo malignancies in renal transplant recipients: the past and present. *Transpl Int* 2006;19:607–620
33. Law BK. Rapamycin: an anti-cancer immunosuppressant? *Crit Rev Oncol Hematol* 2005;56:47–60
34. Luan FL, Hojo M, Maluccio M, Yamaji K, Suthanthiran M. Rapamycin blocks tumor progression: unlinking immunosuppression from antitumor efficacy. *Transplantation* 2002;73:1565–1572
35. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005;80:883–889
36. Campistol JM, Gutierrez-Dalmau A, Torregrosa JV. Conversion to sirolimus: a successful treatment for post-transplantation Kaposi's sarcoma. *Transplantation* 2004;77:760–762
37. Monaco A. The role of mTOR inhibitors in the management of post-transplant malignancy. *Transplantation* 2009;87:157–163