CIRUGÍA ESPAÑOLA

www.elsevier.es/cirugia

Original article

Incidence and Survival Rate of *de novo* Tumors in Liver Transplants☆

Carmen Bernal Bellido, Gonzalo Suárez Artacho, José María Álamo Martínez, Luis Miguel Marin Gómez, Carmen Cepeda Franco, Lydia Barrera Pulido, Juan Manuel Praena Fernández, Javier Padillo Ruiz, Miguel Ángel Gómez Bravo*

Hospital Universitario Virgen del Rocío, Sevilla, Spain

ARTICLE INFO

Article history:
Received 21 December 2017
Accepted 4 May 2018
Available online 13 October 2018

Keywords:
De novo malignancies
Liver transplantation
Incidence
Survival analysis

ABSTRACT

Introduction: The greater survival of transplanted patients is accompanied by an increase in the rate of *de novo* malignancies (NM), which are the most frequent late-onset complication. We can distinguish between non-melanoma skin cancers (NMSC), post-transplant lymphoproliferative disorders (PTLD) and solid organ cancers (SOC). Our objective is to determine the incidence of the different types of NM, the time elapsed until diagnosis and survival rates in our setting.

Methods: We conducted a retrospective study of 1071 liver transplant patients from 1990 to 2015 at our center. We analyzed the demographic variables, incidence of NM and survival.

Results: 184 NM developed in 1071 transplant patients (17%), specifically 19% of the males and 13% of the females ($P = .004$). The most frequent NM were NMSC (29%), lung (18%), head and neck (16%), PTLD (10%) and gastrointestinal (8%). The median time of diagnosis was 7.9 years in NMSC, 3.9 years in PTLD and 9.8 years in SOC. Patients with NMSC had significantly better survival than those with PTLD or SOC. The incidence of *de novo* tumors (excluding NMSC) was 1889/100,000 transplants/year. By gender, lung cancer was the most common TOS in men and breast cancer in women.

Conclusion: In our setting, excluding NMSC, the incidence is 8.8 times greater than estimations for the general population, with a high rate of lung cancer, so we should implement preventive and diagnostic strategies.

☆ Please cite this article as: Bernal Bellido C, Suárez Artacho G, Álamo Martínez JM, Marin Gómez LM, Cepeda Franco C, Barrera Pulido L, et al. Incidencia y supervivencia de los tumores *de novo* en trasplante hepático. Cir Esp. 2018;96:501–507.

* *Corresponding author.*
E-mail address: cbernalb@hotmail.com (C. Bernal Bellido).

2173-5077/

Incidencia y supervivencia de los tumores *de novo* en el trasplante hepático

Palabras clave:
Tumor *de novo*
Trasplante hepático
Incidencia
Análisis de supervivencia

RESUMEN

Introducción: La mayor supervivencia del paciente trasplantado viene acompañada del aumento en la tasa de *tumores de novo* (TN) que representan la complicación tardía más frecuente. Podemos distinguir entre tumores de piel no melanoma (TPNM), síndrome linfoproliferativo postrasplante (SLPT) y tumores de órgano sólido (TOS). Nuestro objetivo es determinar la incidencia de los distintos TN, el tiempo trascurrido hasta su diagnóstico y su supervivencia en nuestro medio.

Material y método: Realizamos un estudio retrospectivo de 1.071 trasplantados hepáticos desde 1990 hasta 2015 en nuestro centro. Analizamos las variables demográficas, la incidencia de TN y la supervivencia.

Resultados: Se desarrollaron 184 TN en 1.071 pacientes trasplantados (17%), en el 19% de los varones y en el 13% de las mujeres ($p = 0{,}004$). Los TN más frecuentes fueron los TPNM (29%), pulmón (18%), cabeza y cuello (16%), SLPT (10%) y gastrointestinales (8%). La mediana del tiempo de diagnóstico fue de 7,9 años en los TPNM, 3,9 años en SLPT y de 9,8 años en TOS. Los pacientes con TPNM tuvieron significativamente mejor supervivencia que aquellos con SLPT o TOS. La incidencia de los tumores *de novo* (excluidos TPNM) fue 1.889/100.000 trasplantados/año. Por género, el cáncer de pulmón fue el TOS más común en varones y el cáncer de mama en mujeres.

Conclusión: En nuestro medio, excluidos los TPNM, la incidencia es 8,8 veces la estimada para la población general, con una alta tasa de cáncer de pulmón por lo que deberíamos implementar estrategias preventivas y diagnósticas.

Introduction

Liver transplantation (LT) has been established as a standard treatment for liver failure, with more than 120,000 procedures to date. One-, 5- and 10-year survival rates have improved significantly in the last 25 years to 83%, 71% and 61%, respectively.[1] The incidence of *de novo* malignant tumors in transplant recipients was first described by Penn and Starzl in 1972.[2] In recent years, its incidence has varied from 2.2% to 26%.[3,4] Studies of large registries[5–8] indicate that transplant recipients are 2–7 times more likely to develop *de novo* malignancies than the general population, which are a frequent cause of mortality.[9,10] Different factors have been involved in the development of these tumors: the immunosuppression used, the time elapsed since the transplant was performed and risk factors generally associated with carcinogenesis (viral infections, smoking, alcohol abuse, *etc.*).

In Spain, according to the Spanish Society of Medical Oncology (SEOM),[11] in the last 20 years, the number of tumors diagnosed in the general population has experienced constant growth, due not only to the population increase, but also to early detection techniques and increased life expectancy. In 2015, the most frequently diagnosed tumors in men were prostate, colorectal and lung, while the most frequent in women were breast, colorectal and uterine. Currently, there is a significant number of published studies conducted in patients treated with different solid organ transplants. The aims of the present study were: 1) to analyze the cumulative incidence and characteristics of *de novo* tumors in patients who have undergone LT in our setting; and 2) to determine survival after diagnosis in order to assess the need for preventive strategies and specific early-diagnosis protocols for this population.

Methods

We performed a retrospective analysis of 1071 adult patients who had received a liver transplant at our institution between 1990 and 2015. The variables analyzed included: recipient age, sex, primary indication, date of transplantation, tumor type, date of diagnosis and date of last follow-up. These data were obtained by reviewing patient medical records. The protocol for tumor screening prior to transplantation included: chest x-ray and abdominal ultrasound (thoracoabdominal computed tomography if alterations were found in previous tests), oral endoscopy and colonoscopy in patients over the age of 50 or at risk for colorectal carcinoma; in women, mammography and cervical cytology were performed.

In the post-transplant follow-up, the diagnosis of *de novo* tumor was established by histological examination of tumor biopsies or surgical sample; precancerous lesions have not been included in the analysis. The biopsy date was designated as the date of diagnosis of the *de novo* tumor. Immunosuppressive treatment at our hospital has varied over the years. Currently, patients follow an induction protocol with tacrolimus, mycophenolate mofetil and corticosteroids, the latter of which are withdrawn early. In patients at high risk for renal dysfunction, basiliximab is used with delayed introduction of calcineurin inhibitors. In transplant patients with hepatocellular carcinoma and criteria for poor expla-

nation prognosis, the calcineurin inhibitor is replaced with an mTOR inhibitor.

Statistical Analysis

The statistical analysis was completed using the SPSS package, version 15.0 (SPSS, Chicago, IL, USA) and R v.3.1.3 (R Development Core Team 2015). The results of the categorical variables are presented as percentages, for the continuous variables as a mean (standard deviation) if they follow a normal distribution and a median (range) according to the asymmetry of the distribution. The categorical variables were analyzed with the chi-square test or Fisher's *F*, and for the difference between continuous variables, Student's *t* was used. The estimates of the incidence of *de novo* tumors have been calculated with software R using the ''survival'' and ''cmprsk'' libraries, considering patient death to be a competitive risk. We analyzed patient survival by age at the time of transplantation, using the median age of our series (54 years) as the cut-off point between both groups. The survival estimates were calculated using the Kaplan–Meier method and the comparison between the groups with the log-rank test. A *P* value $< .05$ was considered statistically significant.

Results

De novo tumors were diagnosed in 184 patients. Table 1 shows the clinical and demographic characteristics of the patients, and Table 2 shows the distribution of the 189 *de novo* tumors developed in 184 patients.

In general, *de novo* tumors in transplant patients were more frequent in men than in women (18.5% *vs* 13.1%; *P* = .004) and in patients over the age of 54 (20.6% *vs* 13.5%; *P* = .002). With a median follow-up of 4.9 years, the detailed analysis of the different tumors showed that non-melanoma skin cancer (NMSC) was the most frequent neoplasm. In NMSC as well as post-transplant lymphoproliferative disorder (PTLD), there were no gender-related differences; however, such differences were observed in solid-organ cancers (SOC). Alcoholic cirrhosis was the most frequent primary indication for transplant in 434 patients (40.5%), and *de novo* tumors were detected in 87 patients (20%) in this group: 61 (14%) SOC (20 head-neck tumors, 19 lung and 6 prostate), 20 NMSC and 6 PTLD.

Fig. 1 shows the one-, 5- and 10-year post-transplant survival rates of our series, which stand at 77.8%, 65.4% and 54.8%, respectively. Survival was lower in the group of patients over the age of 54 (75%, 61%, 48% for one-, 5- and 10-year survival, respectively) with no statistically significant differences compared to the group of patients under 54 (81%, 71%, 62% for one-, 5- and 10-year survival, respectively). Survival after diagnosis varied according to the type of tumor (NMSC, PTLD and SOC) (*P* = .000). As seen in Fig. 2, patients with NMSC had significantly better survival than those with PTLD or SOC. Fig. 3 shows that the incidence of NMSC increased over the years of follow-up and that there were differences between the age groups (*P* = .0001). NMSC developed in 54 patients (5%). In 31 patients, the type was basal-cell carcinoma, in 12 squamous cell carcinoma, in 9 patents both types of tumors, and in one patient a Kaposi's tumor was identified. The median time before diagnosis was 7.9 years (0.3–15.4). The one-, 5- and 10-year survival rates after diagnosis were 100%, 83.1% and 79%, respectively.

Table 1 – Clinical and Demographic Characteristics of Liver Transplant Patients.

Included patients		1071
Age (years)		
Mean		52.1 ± 9.9
Median (range)		54 (14–69)
Follow-up (years)		
Mean (SD)		6.5 (5.9)
Median (range)		4.9 (0–25)
	Patients (%)	*De novo* tumors (%)
Sex		
Male	811 (75.7)	150 (18.5)
Female	260 (24.3)	34 (13.1)
Age		
<54 years	524 (49)	71 (13.5)
>54 years	547 (51)	113 (20.6)
Indication for transplant		
Alcohol-related cirrhosis	434 (40.5)	87 (20)
Viral cirrhosis	428 (39.9)	65 (15.1)
HCV	318 (29.7)	40 (12.5)
HBV	110 (10.2)	25 (22.7)
Cholestatic diseases	56 (5.2)	10 (17.8)
NAFLD	15 (1.4)	2 (13.3)
ALD	22 (2)	2 (9)
Other	117 (10.9)	18 (15.4)
HCC	237(22.1)	14 (6.4)

HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty-liver disease; ALD, acute liver failure; HBV, hepatitis B virus; HCV, hepatitis C virus.

Post-transplant lymphoproliferative syndrome was diagnosed in 18 patients, with a mean recipient age of 52. As shown in Fig. 4, its incidence increased with follow-up time, especially in younger patients, but without reaching statistically significant differences. The median time for diagnosis was 3.9 years (0.1–12.3). Table 3 shows the characteristics of the patients diagnosed with PTLD. In 6 patients, we found an association with the Epstein–Barr virus (EBV), while in 4 patients PTLD developed in the first year after transplantation. The one-, 5- and 10-year survival rates after diagnosis were 63.8%, 33% and 16.8%, respectively.

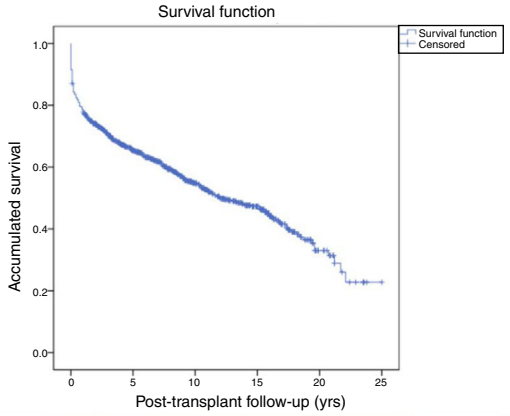
A total of 118 *de novo* solid organ tumors developed in 115 patients (12%): 97 men (13.3%), and 18 women (7.7%) (*P* = .0086). The median time before diagnosis was 9.8 years (0.1–21). Fig. 5 demonstrates how the incidence increased with the follow-up time and was greater in the group of patients over the age of 54 (*P* = .0001), as 28% of patients >54 years had 20 years of follow-up. One-, 5- and 10-year survival rates after diagnosis were 64.7%, 34.9% and 25.4%, respectively, with differences in the different diagnosed tumor types (*P* = .000).

The most frequent solid organ tumors were lung tumors (29%), followed by tumors of the head and neck (25.6%) and gastrointestinal tumors (12%). Fig. 6 shows the survival after tumor diagnosis of the most frequent SOC: - Lung tumors: the overall incidence was 3.1% and was higher in men than in women (3.8% *vs* 1.1%; *P* = .01), with a median time before

Table 2 – Distribution of *de novo* Tumors in Liver Transplant Patients.

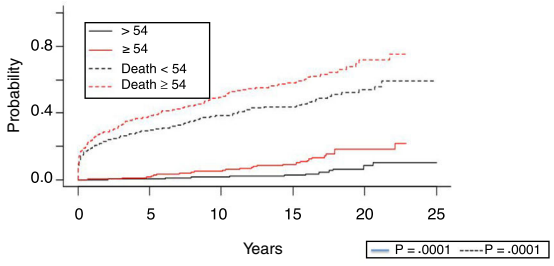
De novo tumors	Total (%)	TN-V (% M)	TN-M (% F)	P value
Non-melanoma skin cancer	54 (28.5)	38 (4.6)	16 (6.1)	.17
Basal-cell carcinoma	40 (21.1)	27 (3.3)	13 (10.5)	.11
Squamous-cell carcinoma	21 (11.1)	18 (2.2)	3 (1.1)	.14
Kaposi's sarcoma	1 (0.5)	0 (0)	1 (0.4)	.12
PTLD	18 (9.5)	14 (1.7)	4 (1.5)	.43
Solid organ tumors	118 (62.4)	104 (12.8)	14 (5.3)	.0004
Lung	34 (18)	31 (3.8)	3 (1.1)	.01
Head and neck	30 (15.8)	28 (3.4)	2 (0.8)	.01
Gastrointestinal	15 (7.9)	11 (1.3)	4 (2.9)	.4
Liver-pancreas	6 (3.2)	6 (0.7)	0 (0)	.1
Breast	5 (2.6)	1 (0.1)	4 (1.5)	.001
Prostate	13 (6.9)	13 (1.6)	0 (0)	.01
Kidney-urothelial	11/5.8)	11 (1.3)	0 (0)	.02
Other	4 (2.1)	3 (0.4)	1 (0.4)	.4
Total	189 (100)	154 (18.9)	34(13.1)	.01

F, females; PTLD, post-transplant lymphoproliferative disorder; M, males.



Follow-up (yrs)	1	5	10	15
Patients at risk	840	524	283	140
Exitus	238	119	70	32

Fig. 1 – Overall survival of liver transplant recipients.



Incidence /100	1	5	10	20
< 54- NMSC	0	0.6	1.7	8.2
> 54- NMSC	0.1	1.7	5.1	18.1
Exitus < 54	19.2	29.6	38.1	53.7
Exitus > 54	24.9	38.3	50	71.7

Fig. 3 – Estimation of the cumulative incidence function of non-melanoma skin cancer (NMSC), according to the different age groups.

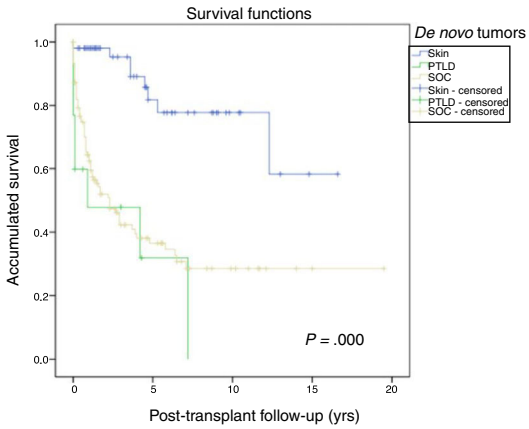
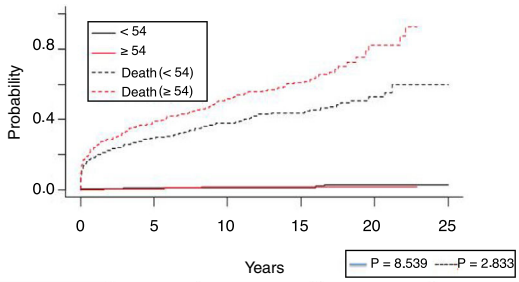


Fig. 2 – Survival after diagnosis of the different *de novo* tumors.



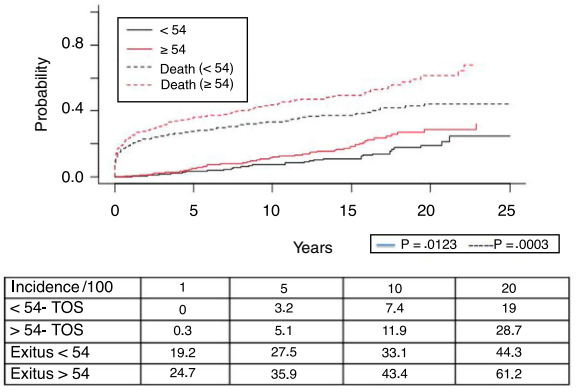
Incidence /100	1	5	10	20
< 54- SLPT	0.5	1	1	2.7
> 54- SLPT	0	0.4	1.3	1.7
Exitus < 54	18.7	29.3	37.9	52.6
Exitus > 54	25.1	38.7	51.5	81.9

Fig. 4 – Incidence of post-transplant lymphoproliferative disorder (PTLD) according to different age groups.

Table 3 – Characteristics of Patients With PTLD.

Patient	Sex	Age (yrs)	LT	EBV recipient	EBV donor	Immunosuppression	WHO categories	Associated with EBV
1	M	48	1991	Positive	Unknown	CSA	Early-stage lesion	Yes
2	M	62	1995	Positive	Unknown	CSA + AZA	Early-stage lesion	Yes
3	M	47	1995	Negative	Unknown	CSA	PTLD monomorphic-B Cell	NC
4	M	49	1998	Positive	Negative	CSA	PTLD monomorphic-B Cell	NC
5	M	44	1999	Positive	Negative	CSA	PTLD monomorphic-B Cell	NC
6	F	50	1999	Negative	Negative	CSA	PTLD monomorphic-B Cell	NC
7	M	20	1999	Positive	Unknown	CSA	Early-stage lesion	Yes
8	F	57	2000	Negative	Unknown	Tacrolimus	PTLD monomorphic-B Cell	NC
9	F	67	2002	Positive	Positive	TAC + MMF	PTLD classic Hodgkin lymphoma	Yes
10	F	52	2004	Positive	Unknown	TAC + MMF	PTLD monomorphic-B Cell	NC
11	M	54	2006	Positive	Unknown	TAC + MMF	PTLD monomorphic-B Cell	NC
12	M	64	2008	Negative	Negative	TAC + MMF	PTLD monomorphic-B Cell	Yes
13	M	54	2009	Positive	Positive	TAC + MMF	PTLD monomorphic-T Cell	NC
14	M	61	2009	Positive	Positive	TAC + MMF	PTLD monomorphic-B Cell	NC
15	M	63	2009	Positive	Unknown	CSA + MMF	PTLD monomorphic-B Cell	NO
16	M	55	2011	Positive	Positive	TAC + MMF	PTLD monomorphic-T Cell	NC
17	M	51	2012	Positive	Unknown	TAC + MMF	PTLD monomorphic-B Cell	NC
18	M	35	2014	Positive	Positive	CSA	PTLD monomorphic-B Cell	Yes

AZA, azathioprine; CSA, cyclosporine; F, female; MMF, mycophenolate mofetil; WHO, World Health Organization; PTLD, post-transplant lymphoproliferative disorder; TAC, tacrolimus; LT, liver transplant; M, male; EBV, virus de Epstein–Barr.



Incidence /100	1	5	10	20
< 54- TOS	0	3.2	7.4	19
> 54- TOS	0.3	5.1	11.9	28.7
Exitus < 54	19.2	27.5	33.1	44.3
Exitus > 54	24.7	35.9	43.4	61.2

Fig. 5 – Incidence of solid organ tumors according to different age groups.

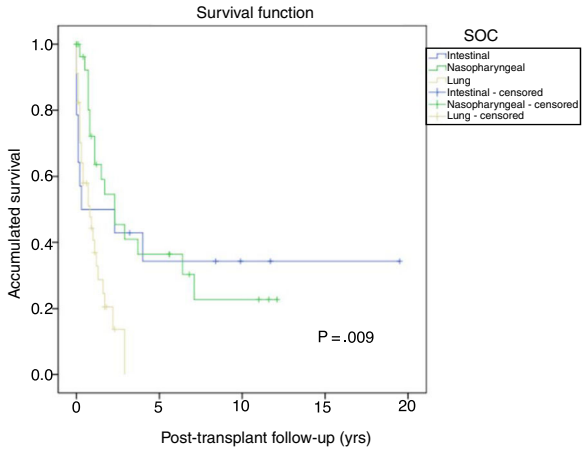


Fig. 6 – Survival after tumor diagnosis for the most frequent SOC.

diagnosis of 6.3 years (0.7–21). The 5-year survival after transplant was 64.7%. The one-, 3- and 5-year survival rates after diagnosis were 44%, 13.5% and 0%, respectively.

- Head and neck tumors: the incidence of these tumors was higher in men than in women (3.4% *vs* 0.8%; $p = 0.01$), with a median time before diagnosis of 3.6 years (0.7–12.7). Five-year survival after transplantation was 56.6%. One-, 3- and 5-year survival rates after diagnosis were 73.2, 43.4% and 34.7%, respectively. - Gastrointestinal tumors: diagnosed in 15 patients with no differences in terms of sex. The most frequent histological type was colon adenocarcinoma in 5 patients (in none was PSC disease the primary indication for LT), followed by 4 gastric tumors, 3 esophageal tumors and one duodenal adenocarcinoma, with a median time before diagnosis of 5.3 years (1.3–19.6). Five-year survival of these patients after transplantation was 80%. One-, 3- and 5-year survival rates after tumor diagnosis were 53.3%, 40% and 32%, respectively. Other tumors, such as prostate adenocarcinoma or breast cancer, had 5-year survivals after diagnosis of 85.5% and 60%, respectively.

Discussion

The cancer data in Spain from 2015 published by the SEOM[11] exclude non-melanoma skin cancer and have an incidence of 215.5 tumors per 100,000 inhabitants. In our series, 132 patients were identified with *de novo* tumors (12.3%) (excluding non-melanoma skin cancer), representing an incidence of 1889.1/100,000 transplanted patients/year, which is 8.8 times greater than in the general population.

This incidence rate is among the highest reported in the literature (2.2%–26%).[3,4] The explanations for the discrepancies include differences in the size of the population studies and duration of follow-up, since the probability of developing these malignant tumors increases after 5 years of follow-up;

therefore, any study with less than 5 years of follow-up underestimates the incidence.[12] The median duration of the follow-up in our cohort is comparable with other reports, so it is likely that our results are influenced by other factors involved (geographical variation, immunosuppressant drugs used and the different methods for identifying and reporting *de novo* malignant tumors).[13,14]

Although the risk factors for the development of malignant neoplasms after LT have not been fully defined, in our setting as well as other studies[15,16] the male gender is significantly associated with an increased risk of cancer.

We agree with the majority of authors that non-melanoma skin cancer is the most frequent *de novo* tumor and that survival after diagnosis does not differ from transplant patients without neoplasms.[4,17,18] Included in this group are squamous-cell cancer (SCC), basal-cell cancer (BCC) and Kaposi's sarcoma. Although it has been reported that the 4/1 ratio of BCC/SCC in the general population seems to be inverted in transplant patients,[19] in our study there is a predominance of BCC with a 2/1 ratio, similar to other national series[4]; nevertheless, we found a median in the time of diagnosis after major transplant (4.1 *vs* 7.9 years). This difference may be due to the decrease in the incidence of skin tumors, especially SCC, in transplant patients in recent decades.[20] In our setting, these tumors are still the most frequent and are not exempt from aggressive behavior. Their main known risk factors (UV radiation, chronic immunosuppression and advanced age) are common in most patients, so the strategies to avoid its appearance are aimed at increasing awareness and the use of sun protection, as well as periodic dermatology revisions of those patients with suspected lesions or a personal history of epithelial cancer.

De novo tumors, excluding non-melanoma skin lesions, are the major cause of mortality in patients transplanted for alcohol-related liver disease.[21] In our setting, this was the most frequent primary indication. *De novo* tumors, excluding skin tumors, developed in 15% of these patients, and more than 50% were aerodigestive tumors. Alcohol and its relationship with a history of smoking have previously been described as the main risk factors.[22–24]

Recipient seronegativity for EBV and incompatibility with donor serology is the main risk factor for PTLD, which includes a broad spectrum of lymphoproliferative disorders. In our setting, Govantes et al.[25] identified 60 PTLD in 5775 kidney transplants from the Andalusian SICATA registry (1990–2009), with a shorter median time until diagnosis of 5.9 years. In our setting, 18 PTLD were identified in 1071 patients, with a shorter median time until diagnosis. This contrasts with series where the rate of PTLD in liver transplant recipients is lower than in other solid organ recipients,[26] while concurring with recent data indicating that liver transplant patients have a higher risk of PTLD compared with renal transplant recipients.[6,27] Hypothetically, the presence of lymphoid tissue in the liver graft could be the contributing factor.[28] We had few cases of PTLD associated with EBV, but the sensitivity of the diagnosis of EBV has changed during the time of the study, so we may have underestimated the actual incidence.

Within the SOC, the incidence of lung cancer varies according to the series (0%–19%).[3,4] In our series, lung cancer was identified in 34 patients and was the most frequent SOC (29%). This incidence is higher than recent publications[8] of multicenter registries that establish the increase of this type of tumor in recent years and differences according to the countries included (it is worth mentioning that 30 lung tumors were identified in 4246 liver transplant recipients). This datum is important because the survival of transplant patients diagnosed with lung tumors is limited, so strategies to reduce the risk of these neoplasms and facilitate their early detection are of utmost importance.

Lastly, we have not found a higher incidence of colon tumors in liver recipients transplanted due to PSC, as has been reported.[8,17] Our pre-transplant screening protocol did not change during the study period and included colonoscopy for patients over 50 years of age or with a history of colorectal cancer risk. Our data do not support considering more frequent colon cancer screening after transplantation than what is already recommended for the general population. In conclusion, this study confirms that transplant patients with *de novo* solid organ tumors have lower survival rates after diagnosis than patients with non-melanoma skin tumors or those with no post-transplant tumors. Our results differ from other published reports, finding a high incidence of lung neoplasms associated with poor prognosis and poor survival. Therefore, we believe that preventive strategies and early detection protocols are justified to detect *de novo* tumors while still in an early and potentially curative stage. The limitations of this study include its retrospective, single-center design, where data on risk factors and the incidence of cancer in our general population have not been validated. As a reference, we have used national data provided by the SEOM.[11]

Authorship

Carmen Bernal Bellido: study design, data collection, analysis and interpretation of the results, article composition and approval of the final version.

José María Álamo Martínez: data collection, analysis and interpretation of the results, critical review.

Gonzalo Suárez Artacho, Luis Miguel Marín Gómez, Carmen Cepeda Franco and Lydia Barrera Pulido: data collection, critical review.

Javier Padillo Ruiz and Miguel Ángel Gómez Bravo: critical review and approval of the final version.

Conflict of Interests

The authors have no conflict of interests to declare.

REFERENCES

1. ELTR-European Liver transplan Registry Website. [accessed 17.12.17]. Available from: http://www.eltr.org/Evolution-of-LTs-in-Europe.html
2. Penn I, Starzl TE. Malignant tumors arising de novo in immunosuppressed organ transplant recipients. Transplantation. 1972;14:407–17.
3. Sanaei AK, Aliakbarian M, Kazemi K, Nikeghbalian S, Shamsa- eefar A, Mehdi SH, et al. De novo malignancy after liver transplant. Exp Clin Transplant. 2015;13:163–6.

4. Herrero JI, Lorenzo M, Quiroga J, Sangro B, Pardo F, Rotellar F, et al. De novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. Liver Transpl. 2005;11:89–97.
5. Engels EA, Pfeiffer RM, Fraumeni JF, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306:1891–901.
6. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: A UK registry audit. Am J Transplant. 2010;10:1889–96.
7. Park HW, Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, et al. De novo malignancies after liver trans-plantation: incidence comparison with the Korean cancer registry. Transplant Proc. 2012;44:802–5.
8. Nordin A, Aberg F, Pukkala E, Pedersen CR, Storm HH, Rasmussen A, et al. Decreasing incidence of cancer after liver transplantation-A Nordic population-based study over 3 decades. Am J Transplant. 2018;18:952–63.
9. Baccarania U, Pisellib P, Serrainoc D, Adania GL, Lorenzina D, Gambatod M, et al. Comparison of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. Dig Liver Dis. 2010;42:55–60.
10. Aberg F, Pukkala E, Hockerstedt K, Sankila R, Isoniemi H. Risk of malignant neoplasms after liver transplantation: a population-based study. Liver Transpl. 2008;14:1428–36.
11. Las cifras del cáncer en España 2017. Sociedad Española de Oncología Médica [accessed 30.10.17]. Available from: https://www.seom.org/es/prensa/el-cancer-en-espanyacom/105941-las-cifras-del-cancer-en-espana-2017
12. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ. Long-term probability of and mortality from de-novo malignancy after liver transplantation. Gastroenterology. 2009;137:2010–7.
13. Mukthinuthalapati PK, Gotur R, Ghabril M. Incidence, risk factors and outcomes of de novo malignancies posliver transplantation. World J Hepatol. 2016;8:533–44.
14. Haagsma EB, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol. 2001;34:84–91.
15. Zhou J, Hu Z, Zhang Q, Li Z, Xiang J, Yan S, et al. Spectrum of de novo cancers and predictors in liver transplantation: analysis of the Scientific Registry of Transplant Recipients Database. PLoS One. 2016;11:e0155179.
16. 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;80:759–64.
17. Yao FY, Gautam M, Palese C, Rebres R, Terrault N, Roberts JP, et al. De novo malignancies following liver transplantation: a case-control study with long-term follow-up. Clin Transplant. 2006;20:617–23.
18. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ. Long-term probability of and mortality from de novo malignancy after liver transplantation. Gastroenterology. 2009;137:2010–7.
19. Modaresi Esfeh J, Hanouneh IA, Dalal D, Tabba A, Lopez R, Pagadala M, et al. The incidence and risk factors of de novo skin cancer in the liver transplant recipients. Int J Organ Transplant Med. 2012;3:157–63.
20. Rizvi SMH, Aagnes B, Holdaas H, Gude E, Boberg KM, Bjørtuft Ø, et al. Long-term change in the risk of skin cancer after organ transplantation: a population-based nationwide cohort study. JAMA Dermatol. 2017;153:1270–7.
21. Cuadrado A, Fábrega E, Casafont F, Pons-Romero F. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl. 2005;11:420–6.
22. Dumortier J, Guillaud O, Adham M, Boucaud C, Delafosse B, Bouffard Y, et al. Negative impact of de novo malignancies rather than alcohol relapse on survival after liver transplantation for alcoholic cirrhosis: a retrospective analysis of 305 patients in a single center. Am J Gastroenterol. 2007;102:1032–41.
23. Jimenez C, Marques E, Loinaz C, Romano DR, Gómez R, Meneu JC, et al. Upper aerodigestive tract and lung tumors after liver transplantation. Transplant Proc. 2003;35:1900–1.
24. Benlloch S, Berenguer M, Prieto M, Moreno R, San Juan F, Rayón M, et al. De novo internal neoplasms after liver transplantation: increased risk and aggressive behavior in recent years? Am J Transplant. 2004;4:596–604.
25. Govantes MA, Esteve AF, Ramos MT, Gracia de Guindo MC, Sánchez LF, Blanca MA, et al. Incidence of post-transplantation lymphoproliferative disease in Andalusia (1990–2009). Transplant Proc. 2013;45:3592–4.
26. Kremers WK, Devarbhavi HC, Wiesner RH, Krom RAF, Macon WR, Habermann TM. Post-transplant lymphoproliferative disorders following liver transplantation: incidence risk factors and survival. Am J Transplantat. 2006;6:1017–24.
27. Dharnidharka VR, Lamb KE, Gregg JA, Meier-Kriesche HU. Associations between EBV serostatus and organ transplant type in PTLD risk: an analysis of the SRTR National Registry Data in the United States. Am J Transplant. 2012;12:976–83.
28. San-Juan R, Comoli P, Caillard S, Moulin B, Hirsch HH, Meylan P, et al. Epstein-Barr virus-related post-transplant lymphoproliferative disorder in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7:109–18.