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Betel quid chewing leads to the development of unique de novo malignancies in liver transplant recipients, a retrospective single center study in Taiwan

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Abstract

Orthotopic liver transplantation (OLT) is the choice of treatment not only for end-stage liver disease and acute liver failure but also for hepatocellular carcinoma (HCC). The development of de novo malignancies after liver transplantation plays an important role in late mortality; the incidence of late mortality has increased owing to improved survival. The incidence of de novo malignancies is 2.3% to 25%, which is 2 to 3 times that of malignancies in the general population. The most commonly reported de novo malignancies in solid organs are skin cancer, Karposi sarcoma, and colon cancer according to the frequency of exposure to a specific carcinogen. We hypothesized that exposure to different carcinogens would change the distribution of de novo malignancies among patients after OLT. In Taiwan, 10% of the population is exposed to a unique carcinogen, the betel quid, which is associated with a high incidence of head and neck cancer (HNC) among the Taiwanese population.

From 2004 to 2014, we retrospectively reviewed 484 cases post-OLT at our institution and 16 patients with 17 de novo malignancies were identified. Most of the patients had HNC, which is in contrast to previous literature reports.

Univariate and multivariate analyses identified betel quid chewing as the main leading factor for HNC in the Taiwanese population.

Routine screening of the oral mucosa in patients with the habit of betel quid chewing is recommended in Taiwan for the early detection of HNC. Routine screening with aggressive treatment after diagnosis of HNC in patients with the habit of chewing betel quid, who underwent OLT, resulted in good patient prognosis.

Abbreviations: CNIs = calcineurin inhibitors, HNC = head and neck cancer, MMF = mycophenolate mofetil, OLT = orthotopic liver transplantation, PTLD = post-transplant lymphoproliferative disorder.

Keywords: betel quid chewing, de novo malignancy, head and neck malignancy, liver transplantation

1. Introduction

Orthotopic liver transplantation (OLT) has had a great impact on patients with end-stage liver disease since the National Institutes of Health' Consensus Development Conference in June 1983[1] and it has also been the most effective treatment for patients with acute liver failure related to virus infection or other etiologies.[2] In patients with HCC, it is the treatment of choice with better disease-free survival compared to other treatments such as hepatectomy and radiofrequency ablation (RFA).[3] Owing to the experience of the surgeon, improvement of perioperative patient care, and the development of better immunosuppression agents, the unadjusted 5-year survival after liver transplantation improved to 72% to 77%.[4] However, complications such as recurrent malignancies or de novo malignancies develop as the long-term survival improves[5] and they become the leading cause of late mortality in patients with functioning grafts after transplantation.[6] Several mechanisms have been proposed to explain the development of malignancies after liver transplantation. The effects of immunosuppression play major roles in the development of de novo malignancies. Immunosuppressive agents exert their effects through the pro-oncogenic calcineurin inhibitors (CNIs), azathioprine and antilymphocyte agents, and decreased tumor suppression owing to the inhibition of natural killer cells and T cells.[7–10]

The incidence of de novo malignancies after OLT reached 2.3% to 25%, which is 2 to 3 times the incidence of malignancies in the general population.[11–20] The incidence of de novo malignancies depends on the length of follow-up, and the most frequently reported malignancies include post-transplant lymphoproliferative disorder (PTLD), skin cancer, Karposi sarcoma, and different kinds of solid organ malignancies.[6,13,16,21–24] The

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real mechanism behind the development of de novo malignancies is still unclear; however, the contributing risk factors include immunosuppression, viral infection, longer survival time, carcinogen exposure such as sunlight, smoking, oncogenic factors transferred from donor, age, and sex. The type of de novo malignancy also depends on the demographics of the transplanted population as well as the different risk factors contributing to the population.[6,25,26] As previously reported, de novo malignancy is a major cause of late mortality in patients undergoing liver transplantation,[6], with a mortality rate of 0.6% to >70%.[5,27,28] Chronically immunocompromised patients would exhibit a rapid progression of the de novo malignancy after detection; therefore, the early evaluation and treatment of suspicious lesions in high-risk patients were suggested to achieve a better treatment effect.[6]

To our knowledge, most studies focusing on the development of de novo malignancies after liver transplantation have been conducted in the European and North American population; therefore, the demographics and risk factors might differ from those of different ethnicities. The effective quantities of immunosuppressive agents also differ between the Western and Eastern physicians. The studies published on the development of de novo malignancies after kidney transplantation showed that the types of malignancies reported in the Asian population differed from those reported in the European and American populations.[29] The patterns of de novo malignancies and the long-term survival after their diagnosis are among our research interests. Therefore, we reviewed the post-liver transplantation patients at our institution for surveillance of the incidence, patterns, and risk factors associated with de novo malignancies after OLT.

2. Patients and methods

We retrospectively reviewed all of the patients who underwent OLT between January 2004 and December 2014 at the Chang Gung Memorial Hospital Linkou. All patients who survived >3 months after OLT were enrolled and they were followed-up until March 2015. The demographic data were retrospectively collected from the medical records and included the age, sex, type of hepatitis, status of liver cirrhosis, indication for liver transplantation, types of OLT, types of de novo malignancies, time elapsed from liver transplantation to the diagnosis of de novo malignancies, treatment of de novo malignancies, and the survival time after the diagnosis of de novo malignancies. All patients were followed-up monthly at the outpatient department of our institution. A routine liver function test was performed and the trough levels of immunosuppressive agents were checked during the follow-up. De novo malignancies were diagnosed based on the results of the histopathological analyses of solid tumor biopsy specimens and the examination of blood smears for the detection of hematological disease. Patients with special risk factors were referred to the relevant department for regular screening. Ethical approval was obtained from the committee of ethics in biomedical research of Chang Gung Memorial Hospital and all experiments were conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

2.1. Immunosuppression

The immunosuppressive agents used at our institution were tacrolimus combined with methylprednisolone and mycophenolate mofetil (MMF). We initially maintained the serum level of tacrolimus at 5 to 10 ng/mL during the first 2 months and reduced it to <5 ng/mL after the first year of liver transplantation. The methylprednisolone was administered intravenously at the ICU for 2 weeks as post-liver transfusion according to the following schedule: day 1, 50 mg; days 2 to 3, 40 mg; days 4 to 6, 30 mg, and days 7 to 14, 20 mg in 2 divided doses. Subsequently, the patients received 15 mg/day of oral corticosteroids in the first month, which was reduced to 2.5 mg/day by the end of 3rd month. Unless the patient developed tacrolimus toxicity or rejection, 1 mg of MMF was administered in 2 divided doses for 3 months. We continued MMF administration until 1 year after the liver transplantation.

2.2. Statistical analysis

Different groups were compared using the Student t test for continuous variables and the Pearson χ^2 test for the categorical variables. A P value <0.05 was considered statistically significant. The risk factors were identified by univariate and multivariate analyses of the data using the Cox regression model. All statistical analyses were performed using the IBM SPSS software version 22.0 (SPSS Inc., Chicago, IL).

3. Results

In total, 484 patients who survived >3 months after liver transplantation at our institution were enrolled. The mean age was 52.5 ± 9.5 years and the patients were predominantly men. Most patients had hepatitis B or hepatitis C infection before transplantation. In total, 17 de novo malignancies were diagnosed in 16 patients with an overall incidence of 3.3%. Table 1 shows the characteristics of patients who underwent liver transplantation.

Among the 17 de novo malignancies, 7 types of malignancies were identified. HNC was the most common diagnosis, followed by PTLD, lung cancer, thyroid cancer, breast cancer, and Bowen disease with 1 case for each cancer, and 1 patient was diagnosed with esophageal cancer after the treatment of tongue cancer. Most patients underwent operation, radiotherapy, chemotherapy, or concurrent chemoradiotherapy after diagnosis. The median follow-up period was 43.3 (3.2–131.2) months, and none of the patients died during the follow-up. The demographic data and clinical features of the patients are shown in Table 2.

Alcohol, smoking, and betel quid chewing were significant risk factors identified by univariate analysis. The result is shown in Table 3. However, multivariate analysis identified only betel quid chewing as a significant risk factor for the development of de novo malignancies. The result is shown in Table 4. The overall survival of patients with de novo malignancies in the present study was better and the rate of late mortality was lower than those reported previously.

4. Discussion

OLT for end-stage liver disease was performed for the first time in 1983[1] and graft rejection decreased dramatically after the introduction of immunosuppressive agents.[30] The 1- and 5-year acceptable survival rates after liver transplantation are 90% and 70%, respectively, worldwide.[4,18] However, improved survival and the long-term use of immunosuppressive agents also contribute to the development of de novo malignancies with reported incidence rates of 2.3% to 25%[11–14,16,17,19] from various registry databases[11–20] and de novo malignancies are

Table 1

Clinical characteristics of patients.

Parameters	N (%)
Study period	2004–2014
No. of patients	484
Age, y, mean ± SD; median (range)	52.5 ± 9.5; 54 (13)
Sex	
Male	358 (74.0)
Female	126 926.0)
Smoking	
No	416 (86.0)
Yes	68 (14.0)
Alcohol	
No	279 (57.6)
Yes	205 (42.4)
Betel quid	
No	467 (96.5)
Yes	17 (3.5)
Hepatitis	
None	93 (19.2)
HBV	262 (54.1)
HCV	106 (21.9)
Dual	23 (4.8)
HCC	
No	263 (54.3)
Yes	221 (45.7)
Malignancy	
No	468 (96.7)
Yes	16 (3.3)
MELD score, mean ± SD; median (IQR)	17.9 ± 9.0; 16 (11)
GRWR (%), mean ± SD; median (IQR)	1.0 ± 0.2; 1.0 (0.3)
Ascites	
No	212 (43.8)
Yes	272 (56.2)
Type of liver transplantation	
Cadaveric	64 (13.2)
Left lobe	36 (7.4)
Right lobe	377 (77.9)
Split	7 (1.4)
Follow up time, mo, median (range)	43.3 (3.2–131.2)
Last follow date	2015/5/31

GRWR = graft/recipient weight ratio, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IQR = interquartile range, MELD = model for end-stage liver disease.

Table 3

Univariant analysis of risk factors.

Parameters	Malignancy		*P*
	No (n = 468)	Yes (n = 16)	
Age, y, median (IQR)	54 (13)	50.5 (10)	0.086
Sex			0.260
Male	344 (73.5)	14 (87.5)	
Female	124 (26.5)	2 (12.5)	
Smoking			<0.0001
No	411 (87.8)	5 (31.3)	
Yes	57 (12.2)	11 (68.7)	
Alcohol			0.001
No	276 (59.0)	3 (18.8)	
Yes	192 (41.0)	13 (81.2)	
Betel quid			<0.0001
No	460 (98.3)	7 (43.8)	
Yes	8 (1.7)	9 (56.3)	
Hepatitis			0.762
None	89 (19.0)	4 (25.0)	
HBV	253 (54.1)	9 (56.3)	
HCV	103 (22.0)	3 (18.8)	
Dual	23 (4.9)	0	
HCC			0.125
No	251 (53.6)	12 (75.0)	
Yes	217 (46.4)	4 (25.0)	
MELD score, median (IQR)	16.0 (11.0)	18.5 (12.8)	0.136
GRWR (%), median (IQR)	0.96 (0.31)	1.01 (0.26)	0.595
Ascites			0.997
No	205 (43.8)	7 (43.8)	
Yes	263 (56.2)	9 (56.3)	
Type of Liver transplantation			0.272
Cadaveric	62 (13.2)	2 (12.5)	
Left lobe	36 (7.7)	0	
Right lobe	364 (77.8)	13 (81.3)	
Split	6 (1.3)	1 (6.3)	

GRWR = graft-recipient weight ratio, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease.

Table 2

Demographics and clinical features of patients with de novo malignancy.

No.	Sex	Age	Primary diagnosis	Hepatitis	Child	MELD	Type of transplantation	Immunosuppression	De novo malignancy	stage	Time to malignancy, mo	Treatment	Follow-up period	Survival
1	Male	51	Alcoholic liver cirrhosis	non	C	26	Cadaveric	Tarcolimus/MMF	Tongue cancer/ esophageal cancer	T1N0M0	77	OP	54	Yes
2	Male	67	HBV/alcoholic liver cirrhosis	B	B	14	Cadaveric	Tarcolimus	Tonsil cancer	T4aN1	110	OP/CCRT	16	Yes
3	Male	50	HBV/alcoholic liver cirrhosis	B	C	25	Cadaveric	Tarcolimus/MMF	Lung cancer	T2aN0	110	OP	5	Yes
4	Male	61	HBV	B	C	14	LDLT	Tarcolimus/MMF	Tongue cancer	T1N2b	15	OP/CCRT	87	Yes
5	Male	54	HCV/alcoholic liver cirrhosis	C	C	17	LDLT	Tarcolimus/MMF	Tongue cancer	T2N2M0	24	CCRT	76	Yes
6	Male	53	HBV	B	B	15	LDLT	Tarcolimus/MMF	CML	N/A	28	CT	60	Yes
7	Male	59	HBV/HCC	B	B	12	LDLT	Tarcolimus/MMF	Tongue cancer	T1N1	76	OP/CCRT	3	Yes
8	Male	67	HBV/HCC	B	B	12	LDLT	Tarcolimus/MMF	Bowen's disease	T2N0	20	OP	59	Yes
9	Male	51	HBV/Alcoholic liver cirrhosis	B	C	18	LDLT	Tarcolimus/MMF	Hypopharyngeal cancer	T4N1	64	CCRT	11	Yes
10	Female	66	HCV/HCC	C	A	11	LDLT	Tarcolimus	Thyroid cancer	T2N0	20	OP	33	Yes
11	Female	72	HCV/HCC	C	C	19	LDLT	Tarcolimus/MMF	Breast cancer	T2N0	31	OP/CT	55	Yes
12	Male	47	HBV	B	C	26	LDLT	Tarcolimus/MMF	Buccal cancer	T3N0	5	OP	52	Yes
13	Male	55	Alcoholic liver cirrhosis	non	B	23	LDLT	Tarcolimus	Tonsil cancer	T3N2B	42	CCRT	11	Yes
14	Male	56	Alcoholic liver cirrhosis	non	C	31	LDLT	Tarcolimus	Hypopharyngeal cancer	T2N1	32	CCRT	6	Yes
15	Male	43	Alcoholic liver cirrhosis	non	B	31	LDLT	Tarcolimus/MMF	Buccal cancer	T4aN2b	32	OP /CCRT	5	Yes
16	Male	48	HBV	B	C	29	LDLT	Tarcolimus/MMF	Tonsil cancer	T2N1	12	CCRT	11	Yes

CCRT = concurrent chemoradiotherapy, CT = chemotherapy, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LDLT = living donor liver transplantation, OP = operation, MMF = mycophenolate mofetil.

Table 4

Multivariate analysis of risk factors of de novo malignancy.

Parameters	OR	95 % CI of OR	*P*
Smoking			
No	1		
Yes	3.94	0.88–17.62	0.072
Alcohol			
No	1		
Yes	1.44	0.29–7.04	0.655
Betel quid			
No	1		
Yes	24.30	5.27–111.93	<0.0001

CI = confidence interval, OR = odds ratio.

the major causes of late mortality among these patients.[6] The incidence of de novo malignancies in the present study was 3.3%, which is lower than the previously reported, with a median follow-up duration of 43.3 months. The incidence of de novo malignancies differs between studies, and the possible explanations for this variation include the sample size of the population, follow-up duration, genetic background that may predispose the population to the development of malignancies, and the exposure to immunosuppressive agents. Notably, a higher incidence rate of de novo malignancies was reported in the Western countries compared to the Eastern countries with incidence rates of 2.3% to 3.2%.[17,19] The patient population at our institution appear to have lower incidence of de novo malignancies after liver transplantation than the patients in the literature databases. Although immunosuppression can be critical in preventing the rejection of graft and maintaining its function as well as in the long-term survival of patients, it also plays a major role in the development of de novo malignancies through its pro-oncogenic effects and decreased tumor suppression owing to the inhibition of natural killer cells and T cells.[7–10] Advances in immunosuppression could help both in the maintenance of lower drug levels and the prevention of graft failure. As we reported in 2014, following the immunosuppression protocol at our institution, the trough level of tacrolimus decreased to 4.00 ± 1.63 ng/mL after 9 months of follow-up in our patients after stabilized liver function post-liver transplantation.[31] Immunosuppressive agents play major roles in the development of de novo malignancies through the suppression of the immune system against cancer and viral infection.[9] Prevention of tacrolimus overexposure was suggested after liver transplantation[10] to reduce the recurrence of HCC.[32,33] The low level of tacrolimus in our patients after their conditions were stabilized might explain the relatively low incidence of de novo malignancies in our patient population.

The reported risk factors for the development of de novo malignancies vary depending on the type of malignancy. PTLD is the most common de novo malignancy, and the risk factors for the development of this malignancy include infection with the Epstein–Barr virus, more immunosuppressive agents, and exposure to OKT3.[34–36] Solid organ malignancies develop more commonly in the first post-transplant year and the risk for developing solid organ malignancies is 2 to 3 times higher in patients who undergo liver transplantation. The risk factors for the development of de novo solid organ malignancies include the age, solar ultraviolet exposure, alcohol, smoking, underlying liver disease, and viral infection (Human herpesvirus type 18, Epstein–Barr virus, hepatitis B, and hepatitis C).[37–39] The most common solid organ malignancy is the skin cancer, followed by colorectal cancer and lung cancer.[25] Patients who undergo liver transplantation receive pre-transplantation screening and assessment to exclude pre-existing malignancies; however, they still have high risk of developing de novo malignancies after transplantation. Other than preventing exposure to known risk factors, regular screening and reassessment are imperative for the early detection and treatment of de novo malignancies.[27]

Eleven of 16 patients (68.7%) in the present study developed HNC, which significantly differed from the previously reported incidence rate for this type of malignancy. According to a large retrospective review, the incidence of HNC is 0.1% to 2%[40,41] and the risk factors for the development of HNC include alcohol consumption and smoking.[41,42] Among the populations with unique betel quid chewing habits, the incidence of HNC in the Taiwanese population is 2 times as high compared to the other populations (9% vs. 2% to 4%, respectively).[43,44] HNC is one of the 10 leading causes of cancer-related deaths in Taiwan and its incidence increased between the years 1982 and 2003 according to the official registry database.[45] The mortality rate for patients with HNC has still been high in the last 2 decades and the survival rate was best determined by the tumor stage.[45] Betel quid chewing is a special risk factor for the development of HNC in Taiwan, and has been observed in approximately 85% of the patients with HNC.[46] Betel quid chewing, alcohol consumption, and smoking are well-documented risk factors for HNC,[47,48] and the International Agency for Research on Cancer declares betel quid alone as a Group 1 carcinogen that contributes to the development of HNC[49]. In Taiwan, betel quid chewing is widespread with an estimated number of 2 million habitual users (10% of the population). In patients enrolled in the present study, univariate analysis identified smoking, alcohol consumption, and betel quid chewing as risk factors for HNC, which is consistent with the results of previous studies. In one report from the Taiwanese database, a 123-fold increased risk for oral cancer was noted when the 3 risk factors were present.[50] However, multivariate risk factor analysis identified betel quid chewing as the only independent risk factor for the development of HNC. This could explain the high incidence of HNC among the liver transplant patients enrolled in the present study. Owing to the small sample size, the other 2 risk factors, smoking and alcohol consumption, might have been masked by the high risk conferred by betel quid chewing and might have become insignificant in the multivariate analysis.

In any case, betel quid chewing is a unique risk factor among patients with HNC in the Taiwanese population. In Taiwan, the betel quid includes the fresh, unripe betel fruit with slaked lime as an essential ingredient, whereas in South-East Asia, the betel fruit is mature.[51,52] In Taiwan, the betel quid is prepared by placing the fresh unripe betel fruit into the betel leaf with red slaked lime. Tobacco chewing is rare among the Taiwanese population; however, those who chew the betel quid commonly have the habit of smoking.[53] Tobacco and betel quid might synergistically act as carcinogens and a case–control study showed that betel quid chewing and smoking increased the risk of oral cancer 28 and 18 times, respectively, whereas the cumulative effect of betel quid chewing, smoking, and alcohol consumption resulted in a 123-fold increase in the risk of oral cancer.[50] The major risk factor reported in the literature is alcohol consumption,[54] and patients with alcoholic cirrhosis have a 25.5 times higher risk of developing oropharyngeal cancer.[55] Betel quid chewing is a unique risk factor for the Taiwanese population and patients who habitually chew betel quid receive regular surveillance before and after liver transplantation, which helps in the early diagnosis of de novo malignancies.

In Taiwan, the incidence and mortality among patients with HNC have increased in the last 2 decades, and the patients with HNC have the lowest 5-year survival rates among those with other common malignancies.[45,56] It is the sixth most common malignancy in Taiwan according to the data of Cancer Registry Annual Report of Taiwan, Health and National Health Insurance Annual Statistics Information Service, Department of Health, Executive Yuan, and ROC Taiwan (http://www.doh.gov.tw/statistic/index.htm). The most important issue affecting the survival of patients with HNC is the cancer stage at diagnosis, which is determined according to the tumor size, lymph node involvement, distant metastasis, and tumor differentiation status.[46] The overall survival for patients with de novo malignancies in the present study was better than the overall survival reported by previous studies.[45] Regular follow-up after OLT allowed early diagnosis and aggressive treatment after diagnosis resulted in good survival among the patients enrolled in the present study. A previous study suggested that regular surveillance, early detection of de novo malignancies, and aggressive treatment could improve the survival outcomes, which would otherwise place de novo malignancies among the leading causes of late mortality in patients who undergo liver transplantation.[6] The excellent outcome achieved in the present study should be attributed not only to the regular survey and aggressive treatment but also to the relatively short follow-up period after treatment. In the previous studies, preoperative surveillance for HNC in patients with alcoholic liver cirrhosis revealed only 0.17% positive findings and it was not cost-effective.[57] However, in the Taiwanese population, betel quid chewing presents as a unique risk factor, which might be more effective than alcohol consumption. Therefore, intensive preoperative surveillance for the early detection of precancerous lesions to prevent further oncological changes owing to the administration of immunosuppressive agents should be beneficial in our population. The Health Promotion Administration of the Ministry of Health and Welfare in Taiwan provides free of charge mucosal examination for 2 years in the population with habitual smoking or betel quid chewing. The visual screening protocol conducted in Taiwan revealed 98.9% sensitivity and 98.7% specificity for people with tobacco use, alcohol consumption, and betel quid chewing.[58] To improve the long-term survival outcomes for patients with HNC and other de novo malignancies, the importance of early detection and optimal treatment should be emphasized.

Therefore, we suggest intensive surveillance by an otolaryngologist after liver transplantation and the avoidance of tobacco use, alcohol consumption, and betel quid chewing.

5. Conclusion

In summary, HNC was the most common de novo malignancy after OLT in the present study, which is different from the reports of previous studies. Betel quid chewing was identified as an independent risk factor of HNC among our patients. Routine screening of oral mucosa and aggressive treatment of HNC in patients who underwent OLT improved the overall survival.

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References

[1] National Institutes of Health Consensus Development Conference Statement: liver transplantation, June 20-23, 1983. Hepatology 1984; 4(1 Suppl):107–10.
[2] Murray KF, Carithers RL. AASLD practice guidelines: evaluation of the patient for liver transplantation. Hepatology 2005;41:1407–32.
[3] Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 2005;25:181–200.
[4] Merion RM. Current status and future of liver transplantation. Semin Liver Dis 2010;30:411–21.
[5] Haagsma EB, Hagens VE, Schaapveld M, et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol 2001;34: 84–91.
[6] Fung JJ, Jain A, Kwak EJ, et al. De novo malignancies after liver transplantation: a major cause of late death. Liver Transpl 2001;7(11 Suppl 1):S109–118.
[7] Engels EA, Pfeiffer RM, Fraumeni JFJr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891–901.
[8] Krynitz B, Edgren G, Lindelof B, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—A Swedish population-based study. Int J Cancer 2013;132: 1429–38.
[9] Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. Immunology 2007;121:1–4.
[10] Rodríguez-Perálvarez M, De la Mata M, Burroughs AK. Liver transplantation: immunosuppression and oncology. Curr Opin Organ Transplant 2014;19:253–60.
[11] Baccarani U, Piselli P, Serraino D, et al. Comparison of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. Dig Liver Dis 2010;42:55–60.
[12] Ettorre GM, Piselli P, Galatioto L, et al. De novo malignancies following liver transplantation: results from a multicentric study in central and southern Italy, 1990–2008. Transplant Proc 2013;45:2729–32.
[13] Marques Medina E, Jimenez Romero C, Gomez de la Camara A, et al. Malignancy after liver transplantation: cumulative risk for development. Transplant Proc 2009;41:2447–9.
[14] Valero JM, Rubio E, Moreno JM, et al. De novo malignancies in liver transplantation. Transplant Proc 2003;35:709–11.
[15] Oo YH, Gunson BK, Lancashire RJ, et al. 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.
[16] Kaneko J, Sugawara Y, Tamura S, et al. De novo malignancies after adult-to-adult living-donor liver transplantation with a malignancy surveillance program: comparison with a Japanese population-based study. Transplantation 2013;95:1142–7.
[17] Park HW, Hwang S, Ahn CS, et al. De novo malignancies after liver transplantation: incidence comparison with the Korean cancer registry. Transplant Proc 2012;44:802–5.
[18] Roberts MS, Angus DC, Bryce CL, et al. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. Liver Transpl 2004;10:886–97.
[19] Yu S, Gao F, Yu J, et al. De novo cancers following liver transplantation: a single center experience in China. PloS One 2014;9:e85651.
[20] Adami J, Gäbel H, Lindelöf B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 2003;89:1221–7.
[21] Chatrath H, Berman K, Vuppalanchi R, et al. De novo malignancy post-liver transplantation: a single center, population controlled study. Clin Transplant 2013;27:582–90.
[22] Yao F, Gautam M, Palese C, et al. De novo malignancies following liver transplantation: a case?control study with long-term follow-up. Clin Transplant 2006;20:617–23.
[23] Åberg F, Pukkala E, Höckerstedt K, et al. Risk of malignant neoplasms after liver transplantation: A population-based study. Liver Transpl 2008;14:1428–36.
[24] Penn I. Kaposi's sarcoma in transplant recipients. Transplantation 1997;64:669–73.
[25] Chak E, Saab S. Risk factors and incidence of de novo malignancy in liver transplant recipients: a systematic review. Liver Int 2010;30:1247–58.
[26] McCaughan GW, Vajdic CM. De novo malignant disease after liver transplantation? Risk and surveillance strategies. Liver Transpl 2013;19 (S2):S62–7.
[27] Chandok N, Watt K. Burden of de novo malignancy in the liver transplant recipient. Liver Transpl 2012;18:1277–89.
[28] Sheil AG. Malignancy following liver transplantation: a report from the Australian Combined Liver Transplant Registry. Transplant Proc 1995;27:1247.
[29] Hsiao F, Hsu W. Epidemiology of post-transplant malignancy in Asian renal transplant recipients: a population-based study. Int Urol Nephrol 2013;46:833–8.

[30] National Institutes of Health Consensus Development Conference Statement: Liver2 Transplantation-June 20–23, 1983. Hepatology 1984;4(S1):107S–10S.
[31] Thorat A, Chou H, Lee C, et al. Effects of converting tacrolimus formulation from twice-daily to once-daily in liver transplantation recipients. BioMed Res Int 2014;2014:1–7.
[32] Vivarelli M, Cucchetti A, Barba G, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors. Annals of Surgery 2008;248:857–62.
[33] Rodríguez-Perálvarez M, Tsochatzis E, Naveas M, et al. Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. J Hepatol 2013;59: 1193–9.
[34] Kremers W, Devarbhavi H, Wiesner R, et al. Post-transplant lymphoproliferative disorders following liver transplantation: incidence, risk factors and survival. Am J Transplantat 2006;6(5p1):1017–24.
[35] Marqués E, Jiménez C, Manrique A, et al. Development of lymphoproliferative disease after liver transplantation. Transplant Proc 2008;40:2988–9.
[36] Saha A, Robertson E. Epstein-barr virus-associated B-cell lymphomas: pathogenesis and clinical outcomes. Clin Cancer Res 2011;17:3056–63.
[37] Watt K, Pedersen R, Kremers W, et al. Long-term probability of and mortality from de novo malignancy after liver transplantation. Gastroenterology 2009;137:2010–7.
[38] Cogliano V, Baan R, Straif K, et al. Preventable exposures associated with human cancers. JNCI 2011;103:1827–39.
[39] Baccarani U, Adani G, Serraino D, et al. De novo tumors are a major cause of late mortality after orthotopic liver transplantation. Transplant Proc 2009;41:1303–5.
[40] Frezza EE, Fung JJ, van Thiel DH. Non-lymphoid cancer after liver transplantation. Hepatogastroenterology 1997;44:1172–81.
[41] Jiménez C, Rodríguez D, Marqués E, et al. De novo tumors after orthotopic liver transplantation. Transplant Proc 2002;34:297–8.
[42] Bellamy C, DiMartini A, Ruppert K, et al. Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence. Transplantation 2001;72:619–26.
[43] Control of oral cancer in developing countriesA WHO meeting. Bull World Health Organ 1984;62:817–30.
[44] Daftary DK, Murti PR, Bhonsole RB, et al. Risk factors and risk markers for oral cancer in high incidence areas of the world. Oral Cancer 1991;2:29–63.
[45] Chen Y, Chang J, Liao C, et al. Head and neck cancer in the betel quid chewing area: recent advances in molecular carcinogenesis. Cancer Sci 2008;99:1507–14.
[46] Liao C, Chang J, Wang H, et al. Analysis of risk factors of predictive local tumor control in oral cavity cancer. Ann Surg Oncol 2007;15:915–22.
[47] Menvielle G. Smoking, alcohol drinking, occupational exposures and social inequalities in hypopharyngeal and laryngeal cancer. Int J Epidemiol 2004;33:799–806.
[48] Choi Skahyo H. Effect of cigarette smoking and alcohol consumption in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Epidemiol 1991;20:878–85.
[49] Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2004;85:1–334.
[50] Liao C, Kang C, Chang J, et al. Survival of second and multiple primary tumors in patients with oral cavity squamous cell carcinoma in the betel quid chewing area. Oral Oncol 2007;43:811–9.
[51] Yang Y, Lee H, Tung S, et al. Epidemiological survey of oral submucous fibrosis and leukoplakia in aborigines of Taiwan. J Oral Pathol Med 2001;30:213–9.
[52] Lee K, Kuo W, Tsai S, et al. Different impact from betel quid, alcohol and cigarette: Risk factors for pharyngeal and laryngeal cancer. Int J Cancer 2005;117:831–6.
[53] Chung C, Yang Y, Wang T, et al. Oral precancerous disorders associated with areca quid chewing, smoking, and alcohol drinking in southern Taiwan. J Oral Pathol Med 2005;34:460–6.
[54] Duvoux C, Delacroix I, Richardet J, et al. Increased incidence of oropharyngeal squamous cell carcinomas after liver transplantation for alcoholic cirrhosis. Transplantation 1999;67:418–21.
[55] Jain A, DiMartini A, Kashyap R, et al. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. Transplantation 2000;70:1335–42.
[56] Clayman GL, Lippman SM, Laramore GE. Jolland JF, Bast RC, Kufe DW, et al. Head and neck cancer. Cancer Medicine. Philadelphia, USA: Williams & Wilkins; 1997. 1645–710.
[57] Dedhia R, Grandis J, Fontes P, et al. Screening for head and neck cancer in liver transplant candidates: A review of 11 years of experience at the University of Pittsburgh. Laryngoscope 2011;122:539–42.
[58] Chang I, Jiang R, Wong Y, et al. Visual screening of oral cavity cancer in a male population: Experience from a medical center. J Chin Med Assoc 2011;74:561–6.