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ORIGINAL ARTICLE

Incidence and risk factors for the development of lung tumors after liver transplantation

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Summary

Tobacco and immunosuppression are risk factors for developing upper aerodigestive and lung tumors after transplantation. This study comprises 701 adult recipients who survived more than 2 months after transplant: 276 patients underwent orthotopic liver transplantation (OLT) for alcoholic cirrhosis (AC) and 425 for nonalcoholic disease. The aim is to analyze the incidence, clinical characteristics, risk factors, and outcome of patients who develop lung malignancies after OLT. Incidence of lung cancer was 2.1% (15 patients): 4.3% (12 patients) in the alcoholic group and 0.7% (three patients) in the nonalcoholic group ($P < 0.001$). Mean time from OLT to tumor diagnosis was 86 months. Thirteen patients were smokers; 12 patients were heavy drinkers; and 11 were drinkers and smokers. Squamous cell carcinoma was diagnosed in nine patients, large cell carcinoma in three, adenocarcinoma in two, and broncoalveolar in one. Tumor staging: 10 patients at stage IV; three at stage IIIB; and two at stage IIB. Tumor resection was performed in one patient, and three also received chemotherapy. Mean survival after tumor diagnosis was 5.4 months. There is a higher risk of lung cancer in smoker patients who have undergone OLT for AC, and have a very poor prognosis because tumors are diagnosed at advanced stages.

Introduction

In the general population, tobacco and alcohol consumption are known risk factors for oral, pharyngeal, laryngeal, esophageal, and upper airway tumors [1–4], and there is a synergistic effect when patients are exposed to both tobacco and drinking, so that the risk of these tumors is more than seven times higher in heavy drinkers and smokers [2–5]. Tobacco smoking is the etiology of more than 90% of lung cancer in men and approximately 50% in women [6], and the risk of lung cancer rises with increasing pack-year consumption, although the duration of smoking has a greater effect than the number of cigarettes [7]. There is no strong evidence to suggest an alcohol-lung cancer association [3] but long-term alcohol intake can induce genetic alterations that potentiate those of tobacco smoke [4]. Cigarette smoking is associated with alterations in the cellular immune system which cause a decrease in the number of natural killer cells [8,9]. In nontransplant patients it is difficult to separate the effects of alcohol and tobacco because heavy drinkers tend to be heavy smokers and vice versa [1,10], and it has been established that heavier drinking persists in smokers after they stop smoking [11], as does heavier smoking in drinkers after they stop drinking [12].

Initially, it was reported that the frequency of tumors that are common in the general population, such as carcinomas of the lung, prostate, breast, and colon and

invasive carcinomas of the uterine cervix is not increased among transplant recipients [13]. However, patients that are evaluated for orthotopic liver transplantation (OLT) have a history of greater tobacco use than the general population [14], and there was a significantly greater pack-year smoking history in the subgroup of patients who had undergone OLT for alcoholic cirrhosis (AC) [15,16]. Smoking and therapeutic immunosuppression may have adverse additive effects [9], and thus the use of immunosuppressors after OLT contributes to the development of *de novo* tumors, especially in patients who have undergone OLT for AC, and have a concomitant long history of alcohol and tobacco consumption. In these cases a significantly higher incidence of upper aerodigestive and lung tumors has been demonstrated [15,17–20]. To our knowledge, some isolated cases of lung tumors after OLT have been reported among overall series of *de novo* tumors [17,20–32], but we did not find any specific or detailed report of this kind of tumor after OLT, for which reason the aim of this study is to analyze the incidence, clinical characteristics, risk factors, and the outcome of liver transplant recipients who developed *de novo* lung tumors.

Patients and methods

Patient selection

We retrospectively reviewed the clinical history of adult recipients who had undergone OLT. Between April 1986 and July 2004, we performed 1000 OLTs on a population of 883 patients. To analyze the true incidence of de lung novo tumors in adult patients (range, 16–70 years) after OLT, we excluded 103 pediatric recipients (under 16 years) and 79 adult recipients who died within 2 months post-OLT. Thus, this study comprises a sample of 701 patients who had undergone OLT: 276 patients (39.4%) for AC group, and 425 patients (60.6%) for acute or chronic non-alcoholic cirrhosis (N-AC group). The diagnosis of *de novo* lung tumors was confirmed by histological examination. This study was closed in October 2005.

Definitions of alcohol and tobacco consumption

Alcoholic cirrhosis was defined as a daily consumption of more than 80 g/day of alcohol over five or more years. Smokers were defined as tobacco consumers for more than 4 years, and were divided into five groups according to cigarettes/day consumption: nonsmokers, minimal (<5 cigarettes/day), light (5–14 cigarettes/day), intermediate (15–24 cigarettes/day), and heavy smokers (≥25 cigarettes/day). Tobacco abuse was also expressed as pack-year consumption.

Immunosuppression

One immunosuppressive regimen consisted of cyclosporine A (CyA), prednisone, and azathioprine or mycophenolate mofetil (MMF), and the other comprised tacrolimus and prednisone. Azathioprine was usually discontinued 3 months after OLT or when leukopenia was evident. From 1996, azathioprine was substituted by MMF. Steroids were generally withdrawn between 3 and 12 months in CyA regimen, and usually at 3 months in tacrolimus regimen. CyA trough levels were maintained between 200 and 300 ng/ml during the first month and progressively decreased to 100–150 ng/ml during the first 6 months. Tacrolimus trough levels were maintained between 10 and 15 ng/ml during the first month, between 8 and 12 ng/ml until the sixth month, and between 5 and 8 ng/ml thereafter.

Acute rejection was initially treated with 1 g of methylprednisolone (MP) intravenously for 3 days, and steroid recycling. Steroid-resistant rejection was also treated with orthoclone OKT3 (OKT3 monoclonal antibody) or antithymocyte globulin (ATG), however in the last 8 years these antibodies have rarely been used, and have been replaced by other therapy options such as increasing doses of tacrolimus, or conversion from CyA to tacrolimus. When adverse events (nephrotoxicity, hypertension, and diabetes) related to calcineurin inhibitors (CNI) were evident, we decreased the doses of CyA or tacrolimus and also added MMF to the immunosuppressive regimen. Conversion from CNI to MMF monotherapy was performed on long-term follow-up recipients who showed severe adverse CNI-related effects but stable liver function.

Post-transplant follow-up

During the first 2 months after OLT, the recipients were followed twice monthly in the outpatient clinic, and monthly thereafter until the sixth month after transplant. After this period, recipients were seen every 2–6 months or at more frequent intervals in cases of complications. Outpatient visit protocol usually included physical examination, laboratory studies (white and red cell blood counts, hemoglobin, liver function and coagulation tests, serum glucose, and creatinine). Other studies [chest X ray, computed tomography (CT) scan, abdominal echo-Doppler, oropharyngolaryngeal examination, broncoscopy, gastroscopy, and colonoscopy] were performed where indicated by symptoms. Recipient follow-up after OLT ranged from 9 to 206 months. The purpose of this study was to analyze the incidence of lung tumors, risk factors (consumption of tobacco and alcohol, immunosuppression regimen, rate of rejection, and treatment), clinical presentation, histologic type and staging [33], surgical therapy, adjuvant chemotherapy, and survival.

Statistical analysis

Data were expressed as mean ± SD. Differences between proportions were assessed by chi-square test. The Kaplan–Meier method was used to calculate the actuarial patient survival curve. $P < 0.05$ was considered statistically significant.

Results

Incidence

A total of 109 *de novo* tumors were observed among 701 recipients, with an overall incidence of 15.5% : 69 tumors (25%) in the AC group ($n = 276$), and 40 tumors (9.4%) in the N-AC group ($n = 425$) ($P < 0.001$). Ten recipients (1.4%) developed two tumors, and one recipient (0.14%) developed three tumors. There were 230 smoker patients (83.3%) in AC group and 183 (43%) in N-AC group ($P < 0.001$). *De novo* lung tumors were detected in 15 of these patients (2.1%): 12 patients (4.3%) in the AC group and three patients (0.7%) in the N-AC group ($P < 0.001$). Thirty-two months before lung tumor diagnosis, one patient was diagnosed of a *de novo* tonsil tumor. There were 14 men (93.3%) and one woman (6.7%) with a mean age at OLT of 50.8 ± 9.6 years (range, 32–63 years). Mean time from OLT to lung tumor diagnosis was 86 ± 43 months (range, 10–184 months), and mean patient age at this time was 58.1 ± 8.1 years (range, 42–72 years). Indications for OLT were as follows: AC in 12 patients, hepatitis C cirrhosis in one patient, hepatitis B cirrhosis in one patient, and acute liver failure caused by hepatitis B in one patient.

Risk factors for lung tumors

Thirteen patients (86.6%) were intermediate or heavy smokers before OLT: 25 ± 12 cigarettes/day (range, 15–60) over 28 ± 11 years (range, 10–45 years), or had a mean 40 ± 33 pack-year smoking history (range, 7.5–135). One patient was minimal smoker (<5 cigarettes/day for 15 years) and another one was no smoker. After OLT, nine of these smoker patients (64.3%) continued smoking five or more cigarettes/day, with a mean consumption of 6.3 ± 3.4 pack-year (range, 1.5–10), until lung tumor diagnosis. Additionally, before OLT, 12 of these patients (80%) were heavy drinkers (>80 g/day), and three (20%) were light drinkers (<50 g/day of alcohol). Eleven patients (73.3%) were both heavy drinkers and intermediate or heavy smokers. Mean alcohol consumption was 171 ± 122 g/day (range, 20–500 g/day), and mean duration was 20.5 ± 8.6 years (range, 6–40 years). Two patients (13.3%) continued alcohol consumption after OLT.

Ten patients were immunosuppressed with CyA, and five patients with tacrolimus. One patient was converted from CyA to tacrolimus because of acute rejection, and another was changed from CyA to MMF monotherapy because of nephrotoxicity. Acute rejection before tumor diagnosis was histologically diagnosed in seven recipients (46.6%): five patients presented one episode that was treated with 1 g of MP for 3 days, and two patients recorded two episodes and received an overall dose of 6 g of MP. One of these patients also received 5 mg/day of OKT3 for 13 days because of steroid-resistant rejection.

Clinical presentation of lung tumors

Fourteen recipients (93.3%) showed one or more symptoms: dyspnea in seven recipients, cough in six, chest pain in two, pleural effusion in two, respiratory insufficiency in two, hemoptysis in one, and headache in one (brain metastasis).

Histology and staging

Histologic subtypes were: nine squamous cell carcinomas (SCCs) (seven in heavy drinkers and smokers, five intermediate, and two heavy smokers of AC group; and two in intermediate smokers in the N-AC group); three large cell carcinomas (two in intermediate and one in heavy smokers in the AC group); two adenocarcinomas (both patients in the AC group: one heavy drinker and smoker, and heavy drinker and minimal smoker), and one bronchoalveolar tumor (nonsmoker patient in the N-AC group). Staging of patients was as follows: 10 patients (66.6%) in stage IV two patients (13.3%) in stage IIB, and three patients (20%) in stage IIIB.

Treatment and patient survival

Only two patients (13.3%) underwent thoracotomy: one patient (6.6%) with bronchoalveolar carcinoma (T3N0M0; stage IIB) underwent resection by left lower lobectomy, and the other patient with large cell carcinoma (T4N0M0; stage IIIB) was unresectable, because of mediastinal involvement. The remaining 13 patients did not undergo exploratory thoracotomy, as they were considered inoperable for several reasons: chronic renal failure and sepsis (one patient with stage IIB), or locally advanced tumor and/or metastatic disease (10 patients in stage IV, and two in stage IIIB). Three patients (20%) received chemotherapy: in one patient as adjuvant treatment after lobectomy, and in two other inoperable patients as a palliative treatment (Table 1).

These patients showed rapid progression of local or metastatic disease, with nine recipients (60%) dying after

Table 1. Clinical characteristics, risk factors, management, and the outcome of patients with lung tumors after OLT.

Cases	Age/sex (OLT)*	Indication OLT	Time to diagnosis (months)†	Histology	TNM (staging)	Pack-year pre-OLT‡	Pack-year post-OLT§	Alcohol intake, g/day (years)¶	IMS regimen	AR episode	AR therapy	Tumor therapy	Outcome/ survival after diagnosis
1	38/M	AC-HBV	184	SCC	T3N2M1 (IV)	30	7.5	85 (20)**	CyA	1	↑ CyA	Inoperable, metastases, and QT	Died/2 months
2	51/M	AC	120	SCC	T2N1M0 (IIB)	25	10	300 (25)**	CyA → MMF	1	3 g MP	Inoperable, renal failure, and sepsis	Died/13 months
3	55/M	AC hydatid	71	SCC	T4N1M0 (IV)	40	5	130 (20)	TAC	1	3 g MP	Inoperable	Died/7 months
4	63/M	AC	65	SCC	T3N1M1 (IV)	70	0	240 (20)	TAC	0	–	Inoperable and metastases	Died/1 month
5	35/M	HBV	106	SCC	T3N1M1 (IV)	15	0	50 (15)	CyA	0	–	Inoperable, metastases, and renal failure	Died/2 months
6	46/M	ALF (HBV)	60	SCC	T4N3M1 (IV)	20	0	50 (20)	TAC	2	6g MP/OKT3	Inoperable, metastases, and QT	Died/6 months
7	63/M	AC-HCV	111	SCC	T3N1M1 (IV)	7.5	9	180 (40)	CyA	0	–	Inoperable and metastases	Died/1 month
8	50/M	AC-HCV	104	SCC	T3N3M1 (IV)	45	0	160 (30)	TAC	0	–	Inoperable and metastases	Died/2 months
9	56/M	AC	51	SCC	T4N3M0 (IIIB)	135	10	500 (7)	CyA	0	–	Inoperable and respiratory insufficiency	Died/5 days
10	54/M	AC	32	LCC	T3N1M1 (IV)	45	3	200 (20)	CyA	0	–	Inoperable and metastases	Died/1 month
11	62/M	AC	10	LCC	T4N0M0 (IIIB)	40	0	200 (30)	TAC	1	3 g MP	Unresectable and exploratory thoracotomy	Died/7 months
12	51/F	AC	70	LCC	T4N2M1 (IV)	15	1.5	100 (20)	CyA → TAC	2	6 g MP	Inoperable and brain metastases	Died/1 month
13	32/M	AC	120	Adenocarcinoma	T3N1M1 (IV)	2.2	2.5	250 (6)	CyA	1	3 g MP	Inoperable, metastases, and renal failure	Died/2 months
14	52/M	AC	111	Adenocarcinoma	T4N2M0 (IIIB)	30	9	100 (20)	CyA	0	–	Inoperable and metastases	Died/3 months
15	55/M	HCV	80	BCA	T3N0M0 (IIB)	0	0	20 (15)	CyA	0	–	Left upper lobectomy	Died/33 months

AC, alcoholic cirrhosis; ALF, acute liver failure; AR, acute rejection; BCA, broncoalveolar carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; IMS, immunosuppression; LCC, large cell carcinoma; MMF, mycophenolate mofetil; MP, methylprednisolone; OLT, orthotopic liver transplantation; QT, chemotherapy; SCC, squamous cell carcinoma; TAC, tacrolimus; TNM, tumor-node-metastasis.

*Mean = 50.8 years, SD = 9.6 years.

†Mean = 86 months, SD = 43 months.

‡Mean = 40 pack/year (p/y), SD = 33 p/y.

§Mean = 6.3 p/y, SD = 3.4 p/y.

¶Mean = 171 g/day (20.5 years), SD = 122 g/day (8.6 years).

**alcoholic recidivism.

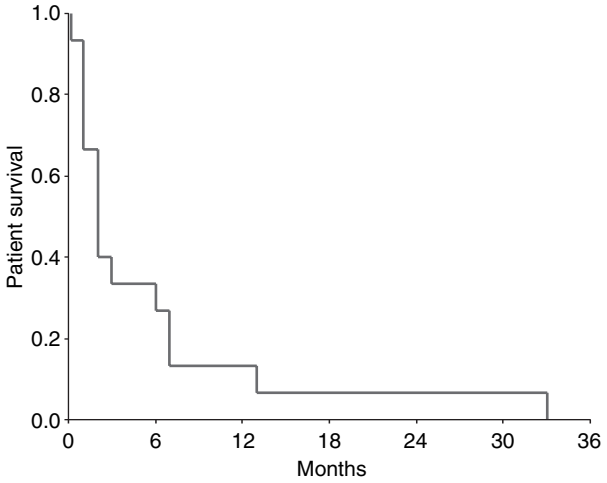

Figure 1 Actuarial patient survival after lung tumor diagnosis.

Table 2. Reported incidence of *de novo* lung tumors after OLT.

First author (reference)	Year of publication	No. of recipients	Cases (incidence, %)	Alive
Levy [21]	1993	556	1 (0.2)	0
Delcambre [22]	1993	88	2 (2.2)	1
Frezza [23]	1997	1657	2 (0.1)	2
Jonas [24]	1997	458	3 (0.6)	1
Jain [17]	1998	1000	8 (0.8)	2
Kelly [25]	1998	888	2 (0.2)	1
Peyregne [26]	1998	251	1 (0.4)	0
Galve [27]	1999	1827	4 (0.2)	NR
Haagsma [28]	2001	174	1 (0.6)	0
Xiol [29]	2001	137	3 (2.2)	NR
Schmilovitz [30]	2003	98	1 (1.0)	0
De Perrot [31]	2003	930	3 (0.3)	1
Benlloch [20]	2004	772	8 (1.0)	NR
Herrero [32]	2005	187	4 (2.1)	2
Overall		9023	43 (0.47)	

Resection rate of *de novo* lung tumors: 11/43 = 25%.

2 months of tumor diagnosis. All patients have now died, and mean survival from tumor diagnosis was 5.4 ± 2.1 months (range, 5 days–33 months). Actuarial patient survival after tumor diagnosis is shown in Fig. 1.

Discussion

The overall incidence of lung cancer in the nontransplant general population of a Spanish community is 21.5 cases per 100 000 (41.6 cases in males and 4.3 cases in females) [34]. In the transplant population there is also a clear preponderance of lung tumors in male patients, explained by the higher rate of males undergoing OLT for AC, usually associated to routine tobacco consumption [17,31,32], as we have borne out in our experience (93%, males). However, the incidence of *de novo* lung tumors after OLT ranged between 0.1% and 2.2% in several reported series [17,20–32] (Table 2), which was similar to our incidence of 2.1%. Thus, our incidence of *de novo* lung tumors is 40-fold higher than that of the general population in Spain. The higher than 2% incidence of lung cancer, detailed in three published series [22,29,32], and which was also our experience, may be explained by the fact that these series only included recipients who survived over 2 months. Other risk factors for the development of lung cancer are: the longer time elapsed since transplant [35]; AC as an indication for transplant [17,20,25]; and a long history of cigarette smoking [17,22,23,25,31,32]. Thus, all recipients with *de novo* lung tumors in several small series [22,23,25,31] have referred the antecedent of heavy smokers, and this addiction or primary risk factor was also present in at least 62.5% of patients from a longer series of eight lung tumors [17] and in 83.3% of our series. In our experience, one additional risk factor which contributes to the development of lung tumor is the continuation of smoking after OLT.

Time elapsed from OLT to tumor diagnosis was reported as between 6 and 71 months, according to several series [21–24,26,28,30–32] with a mean of 48 months in the Pittsburgh series [17], and a longer mean interval of 83 months in our own experience. The mean age of our patients at the time of lung tumor diagnosis was 57.7 years, significantly lower than a Spanish nontransplant population series where lung cancer was diagnosed at a mean age of 67 years [34].

Long-term use of CNI are associated with post-transplant tumors, because of the aberrant production of cytokines that regulate the processes which promote tumor growth, metastasis, and angiogenesis [36], and it has been reported that CyA and tacrolimus exert a similar influence over the development of *de novo* tumors [24]. The use of OKT3 or ATG correlates with the development of *de novo* tumors [22,24], although in our experience only one of our recipients was treated with OKT3. On the other hand, rapamycin has recently been shown to have anticancer effects through a mechanism which blocks angiogenesis, and thus the beneficial use of this immunosuppressor in recipients with *de novo* tumors has been suggested. MMF may also posses some antineoplastic properties but this effect has to be confirmed by future studies [36].

All histological lung tumor subtypes have been described [17,24], although SCC and adenocarcinoma predominate, and are both especially frequent in smokers [17,22–24,31,32]. Most histopathologic types in our experience were also SSC and adenocarcinomas but we also found three cases of large cell carcinoma.

There is little reported data on the clinical presentation of *de novo* lung tumors after OLT, however as in our experience, the most common symptoms are similar to those of the nontransplant population; usually dyspnea, cough, fever, hemoptysis, chest pain, pleural effusion, pneumonia, respiratory insufficiency, weigh loss, and headache (brain metastases), while on occasions patients are asymptomatic and diagnosis is made as an incidental finding in the course of a routine chest X ray or CT scan [17,31].

Lung tumors after OLT are usually diagnosed at advanced stages [17,24,32], as we confirmed in our series, where 10 patients (66.6%) were classified as stage IV, three patients (20%) as stage IIIB, and two patients (13.3%) as stage IIB. This finding was similar to that of De Perrot *et al.* [31], considering both their experience and the literature reviewed on lung tumors after solid organ transplants, where almost two-thirds of cases were also diagnosed at an advanced stage. To obtain early detection at a potentially curable stage of lung cancer, the goal is to perform screening with CT scan every year in recipients at higher risk, especially in older recipients, over-immunosuppressed cases, and patients of more than 20–30 pack-year smoking history who have undergone OLT for AC [16,31,32,37,38].

In a recent study [39] using CT screening in 28 689 asymptomatic nontransplant population with a mean age of 61 years, and median of 30 pack-year smoking history, were diagnosed 436 cases of nonsmall cell lung cancers: 85% with no metastases (N0M0), and 91%, 83%, 68%, and 55% for the respective size categories of 15 mm or smaller, 16–25 mm, 26–35 mm, and 36 mm or greater. Then, with this approach is possible to diagnose lung tumors at early stages with the option of surgical resection and better prognosis.

In a series of nontransplant patients, the rate of surgical resection for all types of lung tumors was 19% and 5-year overall survival was 7.9%: 2.8% for small cell cancer and 9.4% for large cell carcinoma [40]. According to both reported liver transplant series [17,22,24,25] and our experience, lung tumor resection can only be performed at early stages (I or II) and when the patients are in good general condition. There is little data on surgical resection of lung tumors after OLT but al least 12 resected cases have been reported from among 43 cases, with a resection rate of 28% [17,22,24,25,31,32]. In our experience 13 cases (86.6%) were classified as stage IIIB or higher, which is almost always inoperable, and only two cases were classified as IIB stage. Surgical resection of the tumor was only possible in one of two cases, which underwent thoracotomy, and the remaining IIB case was inoperable because of renal insufficiency and sepsis. Similar results to our series were reported in two series of lung tumors after heart transplantation [9,41]. In a review of the literature on liver transplant recipients [17,20–32] we found only one patient of 43 years (2.3%) that survived more than 5 years after tumor resection [17], a rate significantly lower than in the nontransplant population.

In unresectable patients palliative chemo- and/or radiotherapy is another option [17,24,26,30,31], however very frequently it is not possible to perform any treatment because of the advanced stage of tumors and the poor condition of these patients.

In conclusion, *de novo* lung tumors have a very poor prognosis, mainly because they are diagnosed in advanced stages, are usually unresectable, and have a poor response to chemo- and/or radiotherapy. Several prevention measures must be undertaken to decrease the incidence, such as pretransplant cessation of alcohol and tobacco consumption as early as possible, and reduction of immunosuppression in patients who have undergone OLT for AC. Furthermore, early detection of the tumor by yearly screening with CT scan should contribute to increasing the resectability and survival of these recipients with lung malignancies.

References

1. Franceschi S, Talamini R, Barra S, *et al.* Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in Northern Italy. *Cancer Res* 1990; **50**: 6502.
2. Mashberg A, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among US veterans. *Cancer* 1993; **72**: 1369.
3. Longnecker MP. Alcohol consumption and risk of cancer in humans: an overview. *Alcohol* 1995; **12**: 87.
4. Castelli E, Hrelia P, Maffei F, *et al.* Indicators of genetic damage in alcoholics: reversibility after alcohol abstinence. *Hepatogastroenterology* 1999; **46**: 1664.
5. Kato I, Nomura AMY. Alcohol in the etiology of upper aerodigestive tract cancer. *Oral Oncol Eur J Cancer* 1994; **30B**: 75.
6. Parkin DM, Pisani P, López AD, Masuyer E. At least one in seven cases of cancer is caused by smoking. *Int J Cancer* 1994; **59**: 494.
7. Sobue T, Yamamoto S, Hara M, Sasazuki S, Sasaki S, Tsugane S. Cigarette smoking and subsequent risk of lung cancer by histologic type in middle-aged Japanese men and women: the JPHC study. *Int J Cancer* 2002; **99**: 245.
8. Tollerud DJ, Clark JW, Brown LM, *et al.* Association of cigarette smoking with decreased numbers of circulating natural killer cells. *Am Rev Respir Dis* 1989; **139**: 194.
9. Goldstein DJ, Austin JHM, Zuech N, *et al.* Carcinoma of the lung after heart transplantation. *Transplantation* 1996; **62**: 772.

10. Shiffman S, Fischer LA, Paty JA, Gnys M, Hickox M, Kassel JD. Drinking and smoking: a field study of their association. *Ann Behav Med* 1994; **16**: 203.
11. Perkins KA, Bohay J, Meylahn EN, Wing RR, Mathews KA, Kuller LH. Diet, alcohol intake, and physical activity as a function of smoking status in middle-aged women. *Health Psychol* 1993; **12**: 410.
12. Keenan RM, Hatsukami DK, Pickens RW, Gust SW, Strelow LJ. The relationship between chronic ethanol exposure and cigarette smoking in the laboratory and natural environment. *Psychopharmacology (Berl)* 1990; **100**: 77.
13. Penn I. Cancers complicating organ transplantation. *N Engl J Med* 1990; **323**: 1767.
14. Ehlers SL, Rodriguez JR, Widows MR, Reed AI, Nelson DR. Tobacco use before and after liver transplantation: a single center survey and implications for clinical practice and research. *Liver Transpl* 2004; **10**: 412.
15. Duvoux C, Delacroix I, Richardet JP, *et al.* Increased incidence of oropharyngeal squamous cell carcinomas after liver transplantation for alcoholic cirrhosis. *Transplantation* 1999; **67**: 418.
16. Jiménez C, Rodríguez D, Marqués E, *et al.* De novo tumors after orthotopic liver transplantation. *Transplant Proc* 2002; **34**: 297.
17. Jain AB, Yee LD, Nalesnik MA, *et al.* Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. *Transplantation* 1998; **66**: 1193.
18. Romano DR, Jiménez C, Rodríguez F, *et al.* Orthotopic liver transplantation in alcoholic cirrhosis. *Transplant Proc* 1999; **31**: 2491.
19. Jiménez C, Marqués E, Loinaz C, *et al.* Upper aerodigestive tract and lung tumors after liver transplantation. *Transplant Proc* 2003; **35**: 1900.
20. Benlloch S, Berenguer M, Prieto M, *et al.* De novo internal neoplasms after liver transplantation: increased risk and aggressive behavior in recent years? *Am J Transplant* 2004; **4**: 596.
21. Levy M, Backman L, Husberg B, *et al.* De novo malignancy following liver transplantation: a single-center study. *Transplant Proc* 1993; **25**: 1397.
22. Delcambre F, Pruvot FR, Ramon P, *et al.* Primary broncogenic carcinoma in transplant recipients. *Transplant Proc* 1996; **28**: 2884.
23. Frezza EE, Fung JJ, Van Thiel DH. Non-lymphoid cancer after liver transplantation. *Hepatogastroenterology* 1997; **44**: 1172.
24. Jonas S, Rayes N, Neumann U, *et al.* 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.
25. Kelly DM, Emre S, Guy SR, Miller CM, Schwartz ME, Sheiner PA. Liver transplant recipients are not at increased risk of nonlymphoid solid organ tumors. *Cancer* 1998; **83**: 1237.
26. Peyrégne V, Ducerf C, Adham M, *et al.* De novo cancer after orthotopic liver transplantation. *Transplant Proc* 1998; **30**: 1484.
27. Galve ML, Cuervas-Mons V, Figueras J, *et al.* Incidence and outcome of de novo malignancies after liver transplantation. *Transplant Proc* 1999; **31**: 1275.
28. Haagsma EB, Hagens VE, Schaapveld M, *et al.* Increased cancer risk after liver transplantation: a population-based study. *J Hepatol* 2001; **34**: 84.
29. Xiol X, Guardiola J, Menendez S, *et al.* Risk factors for development of de novo neoplasia after liver transplantation. *Liver Transpl* 2001; **7**: 971.
30. Schmilovitz-Weiss H, Mor E, Sulkes J, *et al.* De novo tumors after liver transplantation: a single-center experience. *Transplant Proc* 2003; **35**: 665.
31. De Perrot M, Wigle DA, Pierre AF, *et al.* Broncogenic carcinoma after solid organ transplantation. *Ann Thorac Surg* 2003; **75**: 367.
32. Herrero JI, Lorenzo M, Quiroga J, *et al.* De novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. *Liver Transpl* 2005; **11**: 89.
33. AJCC. Cancer staging handbook. Lung. In: Greene FL, Page DL, Fleming ID, eds. *AJCC Cancer Staging Manual*, 6th edn. New York: Springer-Verlag, 2002: 191–203.
34. Estudio del Carcinoma Broncopulmonar de la SOCALPAR. Incidencia del carcinoma broncopulmonar en Castilla-León durante el año 1997. Estudio multicéntrico de la Sociedad Castellano-Leonesa de Patología Respiratoria (SOCALPAR). *Arch Bronconeumol* 2000; **36**: 313.
35. Fung JJ, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B. De novo malignancies after liver transplantation: a major cause of late death. *Liver Transpl* 2001; **7**: S109.
36. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation* 2004; **77**: 1777.
37. Arcasoy SM, Hersh G, Christie JD, *et al.* Broncogenic carcinoma complicating lung transplantation. *J Heart Lung Transplant* 2001; **20**: 1044.
38. Rosenbaum DH, Bhojani RA, Dikmen E, *et al.* Routine computed tomography screening of the chest in high-risk cardiac transplant recipients may improved survival. *J Heart Lung Transplant* 2005; **24**: 2043.
39. The International Early Lung Cancer Action Program Investigators. Computed tomographic screening for lung cancer. The relationship of disease stage to tumor size. *Arch Intern Med* 2006; **166**: 321.
40. Sanchez de Coss J, Disdier C, Corral J, Riesco JA, Sojo MA, Masa JF. Overall long-term survival in lung cancer analyzed in 610 unselected patients. *Arch Bronconeumol* 2004; **40**: 268.
41. Pham SM, Kormos RL, Landreneau RJ, *et al.* Solid tumors after heart transplantation: lethality of lung cancer. *Ann Thorac Surg* 1995; **60**: 1623.

