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# Lung cancer after heart transplantation: results from a large multicenter registry

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**Abstract**

In this study we analyzed Spanish Post-Heart-Transplant Tumour Registry data for adult heart transplantation (HT) patients since 1984. Median post-HT follow-up of 4357 patients was 6.7 years. Lung cancer (mainly squamous cell or adenocarcinoma) was diagnosed in 102 (14.0% of patients developing cancers) a mean 6.4 years post-HT. Incidence increased with age at HT from 149 per 100 000 person-years among under-45s to 542 among over-64s; was 4.6 times greater among men than women; and was four times greater among pre-HT smokers (2169 patients) than nonsmokers (2188). The incidence rates in age-at-diagnosis groups with more than one case were significantly greater than GLOBOCAN 2002 estimates for the general Spanish population, and comparison with published data on smoking and lung cancer in the general population suggests that this increase was not due to a greater prevalence of smokers or former smokers among HT patients. Curative surgery, performed in 21 of the 28 operable cases, increased Kaplan–Meier 2−year survival to 70% versus 16% among inoperable patients.

**Abbreviations**: HT, heart transplantation; SPHTTR, Spanish Post-Heart-Transplant Tumour Registry; NCNL, noncutaneous nonlymphomatous; Cis, confidence intervals; SIRs, standard incidence rates; Pys, person-years; NOS, not otherwise specified; ASR, age-standardized overall rates

## Introduction

In the world as a whole, lung cancer is the commonest malignancy bar breast or prostate cancer; in Europe it is the commonest bar these and colorectal cancer, and estimates for Spain show the same situation (1). Among patients who have undergone heart transplantation (HT), lung cancer is the second commonest malignancy, approximately *ex aequo* with lymphomas and behind skin cancers, which account for about 50% of the total (2,3). Whereas it is well attested that the incidence of lymphoma and skin cancer among HT patients is higher than in the general population (see, for example, Jensen et al. (4); Swerdlow et al. (5); Roithmaier et al. (6)), studies of post-HT lung cancer have produced discrepant results in this regard (6–9).

The Spanish Post-Heart-Transplant Tumour Registry (SPHTTR) continually updates data on tumors in all patients who have undergone HT in Spain since the initiation of HT in this country in 1984. Here we report on an analysis of SPHTTR data for adult post-HT lung cancer with regard to its incidence (overall and among various patient subgroups), its characteristics, the treatment given and survival.

Methods

The SPHTTR contains records for 5301 patients who underwent HT in Spain between 1984 and the end of 2008 when aged > 15 years. Of these, we excluded from this study 942 who died within 3 months of HT and two who underwent HT on December 31 2008. Of the 4357 included, 3648 (83.7%) were men aged 51.8 ± 10.9 years at HT and 709 women aged 50.2 ± 12.3 years at HT.

For determination of the incidence of lung cancer in various groups, the data considered were sex, age at HT, age at diagnosis of lung cancer, pre-HT smoking history, development of any tumor, development of a noncutaneous nonlymphomatous (NCNL) tumor, development of lung cancer and duration of follow-up (terminated at the earlier of death or December 31st 2008). For characterization of post-HT lung cancer, additional variables considered were the time between HT and diagnosis, the histopathological characteristics of the tumor, whether it was disseminated or localized at diagnosis, surgery (curative, palliative or none) and postdiagnosis survival.

Total incidence (age-standardized for the world standard population aged > 15 years (10)), and incidence in age-at-diagnosis groups (16–44, 45–54, 55–64 and ≥ 65 years), were compared with GLOBOCAN 2002 estimates for the general Spanish population (11). The discrepancy between the age of initiation of adulthood used in the SPHTTR (16 years) and the lower limit of the 15–44 years age group used for the world standard population is deemed of no consequence in this study. Confidence intervals (CIs) for incidence rates in HT patient age groups were calculated using the quadratic approximation to the Poisson log likelihood for the log rate parameter (12). CIs for GLOBOCAN 2002 age-group-specific incidence rate estimates, and the statistical significance of rate ratios, were calculated as described by Rosner (13) using Epidat 3.1 (14). CIs for age-standardized overall incidence rates were calculated as per Fay and Feuer (15) using Epidat 3.1.

Incidence was related to age at HT by means of a Poisson regression analysis. Postdiagnosis survival curves were constructed by the Kaplan–Meier method and were compared using log rank tests to estimate the statistical significance of differences.

Except where otherwise stated, all statistical calculations were performed using Stata v10.0.

This research protocol was approved by the institutional review board of each participating center.

## Results

Total follow-up of the patients included in the study was 26 989.6 person-years (pys) for the 3648 men (median individual follow-up time 6.8 years), and 5044.0 pys for the 709 women (median 6.5 years). Of all 4357 patients, 729 (16.7%) developed 997 tumors, of which 103 (10.3%) in 102 patients (14.0% of patients developing cancers, 2.3% of all patients) were lung cancers. Lung cancers constituted 25.8% of all NCNL malignancies. In what follows, only the first of the lung tumors developed by the patient who developed two is considered in the analyses.

Ninety-eight of the 102 patients with lung cancer (96%) were men. Among all 102, age at HT ranged from 37 to 72 years (mean 55.3, SD 7.9 years), with twelve patients aged < 45 years, thirty 45–54 years, fifty 55–64 years and ten ≥ 65 years. Eighty of the 102 (78%) had a pre-HT history of smoking; 11 had previously developed other post-HT tumors (which for 9 of the 11 included cancers of the skin, including one case of melanoma); and four developed other primary cancers following the appearance of lung cancer (all four NCNL tumors).

The incidence among male patients was 4.6 times that among women, 363.1 per 100 000 pys as against 79.3 ($p < 0.001$); see Table 1. Incidence increased with age at HT at a compound rate of almost 5% per year (incidence rate ratio 1.0469, $p < 0.001$), from an average 149 per 100 000 pys among under-45s to 542 among over-64s. Among men, incidence increased with age at diagnosis, but the rate ratio relative to the corresponding GLOBOCAN 2002 estimate for the general Spanish population fell from 4.5 for under-45s to 1.8 for over-64s, although these ratios were statistically significant ($p \leq 0.0002$) for all groups other than the under-45s (in which group only one case of lung cancer occurred); the age-standardized rate ratio was 2.18 (Figure 1). The small number of cases among women limited the accuracy of rate and rate ratio estimates, but even so the rate ratio for the 55–64 year age group, 8.4, was statistically significant ($p < 0.05$).

Table 1. Incidence of lung cancer per 100 000 person-years among heart transplantation patients and subgroups defined by sex, age at transplantation or pretransplantation smoking behavior, with incidence rate ratios or relative risk where appropriate and 95% confidence intervals in parentheses.

**Table 1**. Incidence of lung cancer per 100 000 person-years among heart transplantation patients and subgroups defined by sex, age at transplantation or pretransplantation smoking behavior, with incidence rate ratios or relative risk where appropriate and 95% confidence intervals in parentheses

| Group | Follow-up (person-years) | Cases | Incidence rate | Relative risk | *p* |
|---|---|---|---|---|---|
| Total | 32 034 | 102 | 318 (262–387) | – | – |
| Sex | | | | | |
| Male | 26 900 | 98 | 363 (298–443) | 4.58 (1.69–12.44) | <0.001 |
| Female | 5044 | 4 | 79 (30–211) | 1 | |
| Age at HT (years) | | | | | |
| <45 | 8040 | 12 | 149 (85–263) | 1 | |
| 45–54 | 9750 | 30 | 308 (215–440) | 2.06 (1.06–4.03) | 0.03 |
| 55–64 | 12 397 | 50 | 403 (306–532) | 2.70 (1.44–5.07) | <0.001 |
| ≥65 | 1846 | 10 | 542 (291–1007) | 3.63 (1.57–8.40) | <0.001 |
| Pre-HT smoking | | | | | |
| No | 16 800 | 22 | 131 (86–199) | 1 | |
| Yes | 15 233 | 80 | 525 (422–654) | 4.01 (2.50–6.43) | <0.001 |

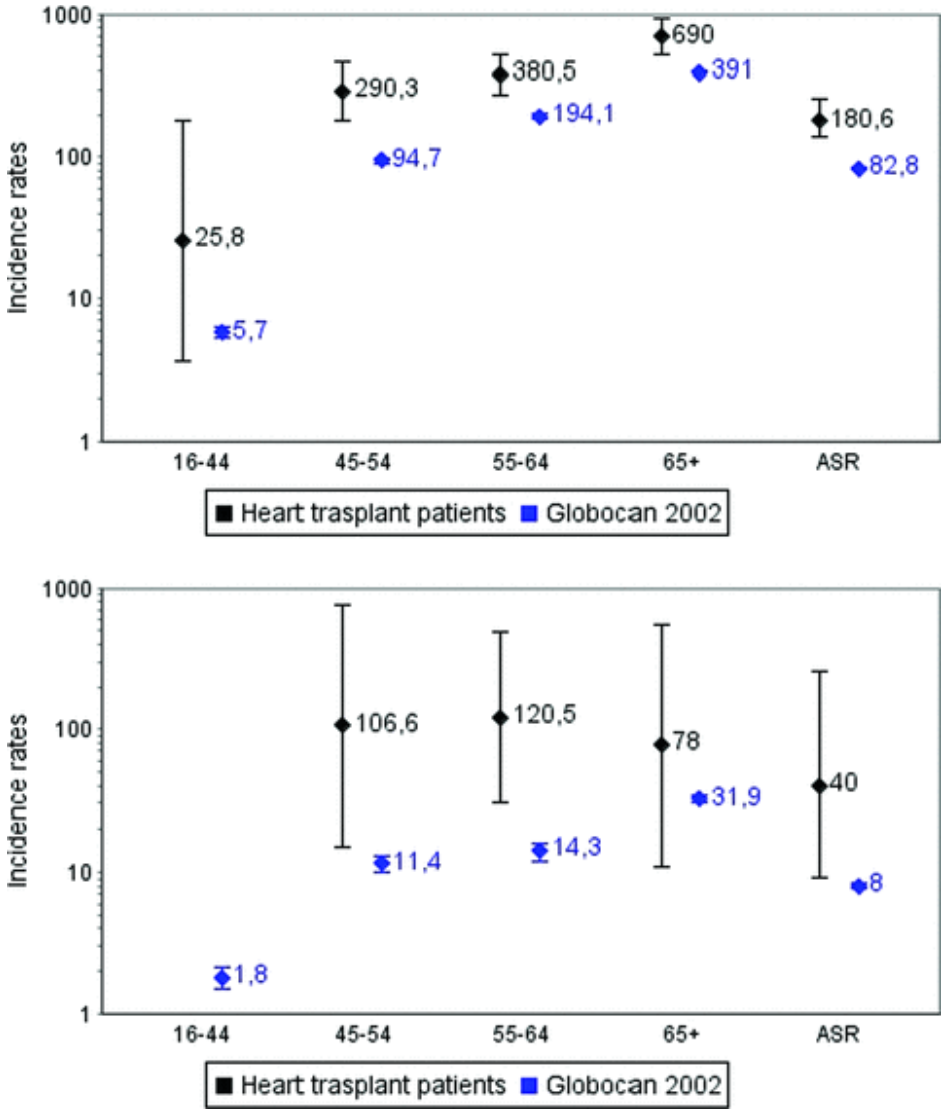


**Figure 1**. Incidence rates per 100 000 person-years in successive age-at-diagnosis groups, and age-standardized overall rates (ASR), for lung cancer among heart transplantation patients (SPHTTR data) and for the general Spanish population (GLOBOCAN 2002 estimates). Whiskers show 95% confidence intervals. Top, men; bottom, women.

The numbers of pre-HT smokers and nonsmokers among the 4357 patients were very similar, 2169 and 2188, respectively. However, with an incidence of 525 per 100 000 pys, pre-HT smokers were four times more likely to develop lung cancer than nonsmokers (incidence 131 per 100 000 pys).

The mean time between HT and diagnosis of lung cancer was 6.4 years (SD 3.7 years, median 5.7 years). At diagnosis, the cancer was disseminated in 79 of the 100 patients for whom information on dissemination status was available, and the main broad histopathological types were squamous cell carcinoma and adenocarcinoma (Table 2). Curative surgery was attempted in 21% of cases, palliative surgery was performed in 7% and 72% were deemed unfit for surgery.

**Table 2**. Characteristics of lung cancer at diagnosis

| | |
|---|---|
| Mean (SD) time since transplantation (years) | 6.36 (3.72) |
| Extent* | |
| Localized | 21 |
| Disseminated | 79 |
| Surgery* | |
| None | 72 |
| Palliative | 7 |
| Curative | 21 |
| Histology** | |
| Epidermoid carcinoma NOS*** | 28 |
| Adenocarcinoma NOS*** | 22 |
| Carcinoma NOS*** | 24 |
| Oat-cell carcinoma (high-grade neuroendocrine carcinoma) | 4 |
| Non-Hodgkin lymphoma | 3 |
| Carcinoid (low-grade neuroendocrine carcinoma) | 1 |
| Sarcoma | 1 |
| T cell lymphoma | 1 |
| Not available | 15 |

*Out of 100 patients for whom relevant data were available.
**Out of 99 patients for whom relevant data were available.
***NOS, not otherwise specified.

Overall Kaplan–Meier survival fell to 26% within 2 years of diagnosis, and 16% after 5 years. There were no statistically significant differences between the survival curves of men and women, or between those of over- and under-55s, or between those of pre−HT smokers and nonsmokers. However, there was a significant difference among the curative surgery, palliative surgery and no surgery groups (p = 0.0004), the curative surgery group having a Kaplan–Meier 2-year survival rate of 70% as against 16% in the no-surgery group (Figure 2).

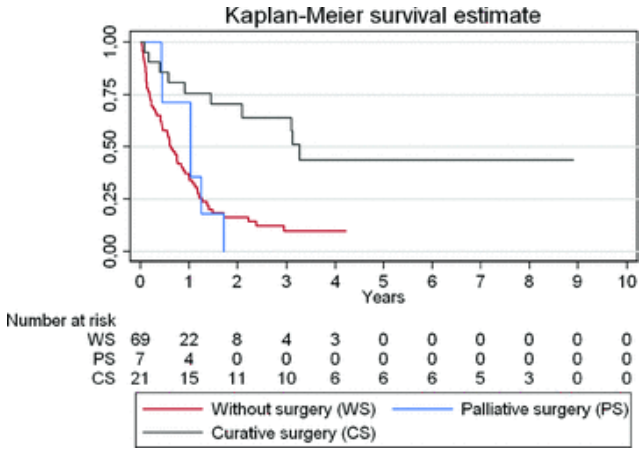


**Figure 2**. Kaplan–Meier estimates of intrinsic survival rates among HT patients following diagnosis of post-HT lung cancer. *(*p = 0.0004).

## Discussion

In this study we found the incidence of lung cancer to be considerably greater among Spanish HT patients than corresponded to GLOBOCAN 2002 estimates for the general Spanish population. Assuming Poisson distributions for cases, the difference was statistically significant in all age-at-diagnosis groups in which more than one case was recorded among HT patients. Although the way in which the GLOBOCAN estimates were constructed doubtless endowed them with a degree of uncertainty over and above the error due to finite sampling, the observed differences, together with the CIs for the incidence rates among HT patients (Figure 1), strongly suggest that the risk of lung cancer is greater among HT patients than in the general population, especially in view of the between-age-group consistency in the sign of the difference.

Similar conclusions have previously been reached by Serraino et al. (9) in northern and central Italy, Jiang et al. (8) in Canada and Collet et al. (16) in the United Kingdom; these authors observed incidence rates among HT patients to be 2.1–2.8 times greater than in the general population. By contrast, a study at Columbia Presbyterian Hospital, New York, found no significant difference between the HT and general populations in regard to the incidence of lung cancer (7). A possible cause of this discrepancy would seem to be Kellerman et al.'s use of a reference population that may have been inappropriate for their HT population. The finding that the incidence of lung cancer is higher among HT patients than in the general population brings this cancer into line with skin cancer (4) and lymphoma (5), and at the same time brings HT patients into line with other solid organ transplant patients (16,17).

Skin cancer was among the post-HT cancers developed by 9 of the 11 patients with post-HT cancers prior to their lung cancer. This finding is in keeping with the known high incidence of skin cancers among HT patients (2,18).

It has been suggested that the high incidence of lung cancer among HT patients—especially in comparison with other cancers without known viral associations—may be largely due to a large proportion of HTs being motivated by cardiopathologies that like lung cancer are favored by smoking, so that HT patients constitute, *a priori*, a population at especially high risk for lung cancer (7,19–21). However, in this study there were marginally fewer pre−HT smokers than nonsmokers, even though 84% of HT patients were men; for this proportion of males, some 62% of patients would be expected to be sometime smokers on the basis of data for the general population of 2001 (22), and probably a larger percentage for earlier years, given the trend for fewer men and more women to be smokers (23). Furthermore, in this study the incidence of lung cancer was only four times greater among pre-HT smokers than among nonsmokers, a relative risk that in the general populations of western nations seems only to be achieved a dozen or more years after cessation of smoking (24,25). It therefore seems likely that in this study the group of pre-HT smokers actually reduced the average risk of HT patients relative to the general population—probably because, as the observed 4:1 ratio suggests, as patients with advanced heart failure they will have ceased smoking several years before HT. We have no information on possible post-HT smoking, but since it would in all probability have tended to inflate the incidence of lung cancer among self-proclaimed former smokers, it would play in favour of our conclusion. Taken together, the above findings thus indicate that although pre-HT smoking certainly increases the risk of lung cancer, as would be expected, the extra risk of HT patients as a class (relative to the general population) is not due to smoking-related bias but has HT-related causes, probably immunosuppression.

That incidence increased with age at HT and with age at diagnosis was to be expected in view of the known age-dependence of the incidence of lung cancer in the general population. However, the incidence rate ratio between the HT and general populations fell with increasing age, the cause of which trend is not clear. One possibility is that, with increasing age, the effect of immunosuppression becomes relatively less due to the gradual decline of the immune system in normal aging.

The mean time between HT and diagnosis of lung cancer, 6.4 years, was similar to the 74 months observed by Bruschi et al. (26) and the 69 months reported by Mohammadi et al. (27), although the median time, 5.7 years, was somewhat shorter than the 7.4 years reported by Anyanwu et al. (21). Although the only cancer staging information included in the SPHTTR is the distinction between localized and disseminated tumors and the indirect information provided by decisions on surgery, our findings also seem to agree with those of Bruschi et al. (26) and others (19,21) as regards lung cancer having frequently been detected only at an advanced stage. Pre−HT smoking had no significant influence on either the median time between HT and diagnosis (pre-HT smokers 5.6 years, nonsmokers 6.0 years) or the proportion of patients who were unfit for curative surgery at diagnosis (pre-HT smokers 80%, nonsmokers 76%).

Although the HT patients in this study differed little from lung cancer patients in general as regards the proportion of cases that were inoperable or only palliatively operable (as also regarding survival), the frequency with which our HT patients underwent check-ups suggests that the disease may advance somewhat more rapidly in HT patients than in others; this idea is in keeping with a report that nonsmall-cell lung cancer tends to be diagnosed at a later stage in organ transplant recipients than in the general

population (28). On the other hand, the lung cancer screening in these check-ups will mostly have been based on chest X-rays, the sensitivity of which for this purpose is notoriously poor. The use of more sensitive techniques is thus desirable both for clarification of tumor aggressiveness and, of course, because of the better prognosis of cases diagnosed early enough to be operable, which has been noted in this study and by others (e.g. Anyanwu et al. (21), Bruschi et al. (26) or Padilla et al. (29)). In particular, in HT follow-up protocols it may be beneficial to replace chest X-rays with low-dose spiral computed tomography (21,26,27), at least on a trial basis. Although the proven sensitivity of spiral CT (The International Early Lung Cancer Action Program Investigators 2006) may be offset in the general population by poor specificity or overdiagnosis—the results of the US NCI National Lung Screening Trial are eagerly awaited—these drawbacks may be less significant in an immunosuppressed population such as HT patients. Recent advances in screening for biomarkers of lung cancer in sputum should also be borne in mind; see, for example, Xing et al. (30) and Varella-García et al. (31).

The major limitations of this study derive firstly from there being no Spanish national cancer registry, which has forced us to use GLOBOCAN estimates for the incidence of lung cancer in the general population; and secondly from the quite coarse nature of the registry data. In particular, the SPHTTR has no staging information for the tumors it records; and although it distinguishes between pre-HT smokers and nonsmokers, it has no information on duration or intensity of smoking, or on date of cessation, or on post-HT smoking.

In spite of the above limitations, we conclude that the incidence of lung cancer among HT patients is greater than in the general population, and that this is not due to a greater prevalence of smokers or former smokers among HT patients (although pre-HT smoking does increase risk). Incidence increases with age, and is greater among men than women. The prognosis is usually dismal due to late detection; early intervention following early detection multiplies the 2-year survival rate by more than four, suggesting that it may be beneficial to employ CT scans in the follow-up of HT patients.

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**Disclosure**

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

**Appendix**

Other investigators involved in maintaining the Spanish Post-Heart Transplant Tumour Registry are as follows: Raquel Marzoa-Rivas and Eduardo Barge-Caballero (Hospital Universitario A Coruña, La Coruña); Jesús Palomo and Fernández-Yáñez (Hospital General Universitario Gregorio Marañón, Madrid); Josep Roca (Hospital Universitario de Bellvitge, Barcelona); Matías Ubilla (Clínica Universitaria de Navarra, Pamplona); Luis Martínez-Dolz (Hospital Universitario La Fe, Valencia); Javier Segovia and Manuel Gómez-Bueno (Clínica Universitaria Puerta de Hierro, Madrid); Vicens Brossa and Marta Campreciós (Hospital de la Santa Creu I Sant Pau, Barcelona); María Martín-Fernández and José L. Rodríguez-Lambert (Hospital Universitario Central de Asturias, Oviedo); Mónica Fernández-Valls (Hospital Universitario Marqués de Valdecilla, Santander); Carmen Segura Saint-Gerons (Hospital Universitario Reina Sofía, Córdoba); Ernesto Lage Gallé (Hospital Universitario Virgen del Rocío, Sevilla); Miguel Ángel Gómez-Sánchez and Pilar Escribano (Hospital Universitario 12 de Octubre, Madrid); Félix Pérez-Villa (Hospital Clinic I Provincial, Barcelona); Maria Luisa Sanz-Julve (Hospital Universitario Miguel Servet, Zaragoza); Iris P. Garrido (Hospital Universitario Virgen de la Arrixaca, Murcia); and Javier López-Díaz (Hospital Clínico Universitario de Valladolid, Valladolid).

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