American Journal of Transplantation. 2008;8:1031-1039

# Malignancy after heart transplantation: incidence, prognosis and risk factors

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**Abstract**

The Spanish Post-Heart-Transplant Tumour Registry comprises data on neoplasia following heart transplantation (HT) for all Spanish HT patients (1984–2003). This retrospective analysis of 3393 patients investigated the incidence and prognosis of neoplasia, and the influence of antiviral prophylaxis. About 50% of post-HT neoplasias were cutaneous, and 10% lymphomas. The cumulative incidence of skin cancers and other nonlymphoma cancers increased with age at HT and with time post-HT (from respectively 5.2 and 8.9 per 1000 person-years in the first year to 14.8 and 12.6 after 10 years), and was greater among men than women. None of these trends held for lymphomas. Induction therapy other than with IL2R-blockers generally increased the risk of neoplasia except when acyclovir was administered prophylactically during the first 3 months post-HT; prophylactic acyclovir halved the risk of lymphoma, regardless of other therapies. Institution of MMF during the first 3 months post-HT reduced the incidence of skin cancer independently of the effects of sex, age group, pre-HT smoking, use of tacrolimus in the first 3 months, induction treatment and antiviral treatment. Five-year survival rates after first tumor diagnosis were 74% for skin cancer, 20% for lymphoma and 32% for other tumors.

## Introduction

A major threat to the long-term survival of heart transplant (HT) patients is malignancy (1–3,4,5). Yet although malignancy has long been known to be favored by immunosuppression (6,7), there has been no systematic evaluation of the impact on post-HT malignancy of the significant advances in immunosuppression and other aspects of posttransplant management that have been made over the past decade or so. Apart from The International Society for Heart & Lung Transplantation (ISHLT) Registry data (2,8) or the Collaborative Transplant Study (CTS) reports (9), there have been few large studies of the incidence and prognosis of neoplasia after HT, or of risk factors for this complication. Most studies have been single-center reports (10–12) or have been unable to estimate incidence because their data sources were registries that only record cases in which neoplasia occurs, such as the Israel Penn International Transplant Tumor Registry (13,14).

Two of the main advances in post-HT management have consisted in the introduction of antiviral prophylaxis and of induction agents that are more specific in their actions. Induction with OKT3 had frequently been blamed for increased incidence of neoplasia, especially posttransplant lymphoproliferative disorder (PTLD) (15), although other studies failed to corroborate such association (11,16,17). Induction is currently used in 40–50% of HTs (2), with agents that block interleukin-2 receptor (IL2R) now largely replacing OKT3. Antiviral prophylaxis with acyclovir or ganciclovir was originally introduced mainly to combat cytomegalovirus, but presumably may also combat viruses associated with some of the neoplasias with most strikingly increased incidence among transplant patients, such as Kaposi's sarcoma (associated with human herpesvirus 8, HHV-8), lymphoproliferative disease (associated with Epstein-Barr virus, EBV) and squamous cell cancers (associated with human papillomavirus, HPV).

The Spanish Post-Heart-Transplant Tumour Registry (SPHTTR) is singular in that its 16 collaborating centers—all the Spanish hospitals performing HTs on adults—continually update it directly with data on tumors in all patients who have undergone HT in Spain since the initiation of heart transplantation in this country in 1984. In this article we discuss the incidence and prognosis of post-HT neoplasia in Spain, and the effects of some possible positive and negative risk factors (including induction treatment and antiviral prophylaxis), as inferred from the SPHTTR record.

## Methods

### *Patients*

A total of 4089 patients aged >15 years who underwent heart transplantation in Spain between 1984 and 31 December 2003 were identified in the SPHTTR. From these were excluded the 695 patients who died in the first 3 months after HT, these deaths being attributed to the surgical procedure (just one of these patients had developed a tumor) and one patient for whom the date of diagnosis of a first post−HT tumor had not been recorded. The remaining 3393 patients were followed up to December 2004.

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

### *Variables*

The outcome data analyzed were the occurrence of post-HT tumors, together with their gross clinical type (skin cancers, lymphomas, others), date of diagnosis, location and histopathology. The treatment variables considered were the use of induction therapy, the agents employed for this purpose, and the duration of treatment; the agents used for maintenance of immunosuppression in each of four post-HT periods (the first 3 months, months 4–12, months 13–24 and later than 2 years post−HT); and the use of antiviral prophylaxis and the agents employed for this purpose. Other possible risk factors considered were sex, pre-HT smoking (information on post-HT smoking was incomplete and was therefore not evaluated) and age at HT (<45, 45–54, 55–64 and ≥65 years). With a view to evaluating the effect of changes in immunosuppressive practice or HT protocols, the era in which HT had been performed was also introduced as an independent variable, the three eras considered being the period before the introduction of mofetil mycophenolate (MMF) (1984–1997), the period between the introduction of MMF and the introduction of IL2R-blockers (1998–2000) and the IL2R-blocker era (2001–2003).

### *Statistical analysis*

For each patient, the number of years at risk was defined as the time between the date of HT and December 2004 or death, whichever occurred first. The incidence, per 1000 person-years, of any kind of tumor, and of each of the three kinds distinguished, was estimated for each sex and age group, and for follow-up to 3 months, 6 months and 1, 2, 3, 4, 5 and 10 years. Univariate risk analyses were performed to estimate the influence of age group, sex, pre-HT smoking, HT era, MMF in the first 3 months, tacrolimus in the first 3 months, induction therapy, induction with OKT3, induction with either equine or rabbit anti-thymocyte globulin (ATG), induction with basiliximab, induction with daclizumab, prophylaxis with acyclovir, prophylaxis with ganciclovir and prophylaxis with either acyclovir or ganciclovir. Multivariate Poisson models were fitted in which the association of tumors with induction in general and with induction by OKT3 and by ATG was evaluated while adjusting for age group, sex, pre-HT smoking and immunosuppression in the first 3 months with MMF and/or tacrolimus, in each of four groups defined on the basis of antiviral prophylaxis: patients given acyclovir, patients not given acyclovir, patients given acyclovir or ganciclovir and patients given neither acyclovir nor ganciclovir. Multivariate analyses were similarly performed to estimate the influence of MMF in the first 3 months on the development of skin cancer, lymphomas and other tumors while adjusting for sex, age group at HT, pre-HT smoking, tacrolimus in the first 3 months, induction therapy and antivirals; and to estimate the influence of tacrolimus in the first 3 months on the development of skin cancer, lymphomas and other tumors while adjusting for sex, age group at HT, pre-HT smoking, MMF in the first 3 months, induction therapy and antivirals.

Kaplan-Meier curves were constructed for survival following first diagnosis of each kind of tumor, and were compared using log-rank tests. These analyses included 482 patients, all those who suffered neoplasia except eight: two whose date of death was unknown, one who was lost to follow-up, and five who had zero post-diagnosis follow-up time, their tumors having been diagnosed post mortem.

The criterion for statistical significance was $p < 0.05$.

## Results

Of the 3393 patients included in this study, 1801 (53.1%) underwent HT in the pre−MMF era (1984–1997), 844 (24.9%) in the period 1998–2000 and 748 (22.1%) in the IL2R-blocker era (2001–2003). Some 84.7% of patients were men, age at the time of transplantation was 51.4 ± 11.0 years, and the median follow-up time was 5.2 years (mean 5.8 years, maximum 20.2 years). By age group, 762 patients (22.5%) were aged <45 years, 1044 (30.8%) between 45 and 54 years, 1365 (40.2%) between 55 and 64 years, and 222 (6.5%)>65 years. Some 48.9% of patients had been smokers before HT.

Data on the use of individual immunosuppressive agents are listed in Table 1. Steroids were used by virtually all patients in the first 3 months post-HT, and by 62.2% after 2 years. The use of cyclosporine and azathioprine declined gradually with increasing time post-HT, while tacrolimus, MMF and sirolimus exhibited the reverse trend. OKT3, ATG, basiliximab and daclizumab were used almost exclusively in the first 3 months post-HT, presumably for induction therapy. On this basis, induction therapy was used in 60.5% of the patients.

**Table 1**. Patients receiving each kind of immunosuppressor (percentages), by period post-HT

| | <3 months | 3–12 months[1] | 1–2 years[2] | After 2 years[2] | At any time |
|---|---|---|---|---|---|
| n | 3,393 | 3,127 | 2,763 | 2,763 | 3,393 |
| Cyclosporine | 79.1 | 73.6 | 73.0 | 64.4 | 84.4 |
| Azathioprine | 60.5 | 53.7 | 54.1 | 42.7 | 68.8 |
| Prednisone | 98.5 | 83.2 | 73.7 | 62.2 | 99.2 |
| Tacrolimus | 8.3 | 12.2 | 12.6 | 17.2 | 21.9 |
| MMF | 25.6 | 28.4 | 27.5 | 40.2 | 48.0 |
| Sirolimus | 0.4 | 0.5 | 0.5 | 6.3 | 6.6 |
| Everolimus | 0.2 | 0.2 | 0.2 | 0.6 | 0.8 |
| OKT3 | 37.4 | 0.2 | 0.0 | 0.2 | 44.3 |
| ATG[3] | 14.3 | 1.7 | 0.4 | 0.3 | 17.1 |
| Basiliximab | 5.6 | 0.0 | 0.0 | 0.0 | 6.7 |
| Daclizumab | 3.4 | 0.0 | 0.0 | 0.0 | 4.1 |

[1]Percentages of the 3127 patients who survived at least 1 year.
[2]Percentages of the 2763 patients who survived at least 2 years.
[3] Includes both equine and rabbit ATG.

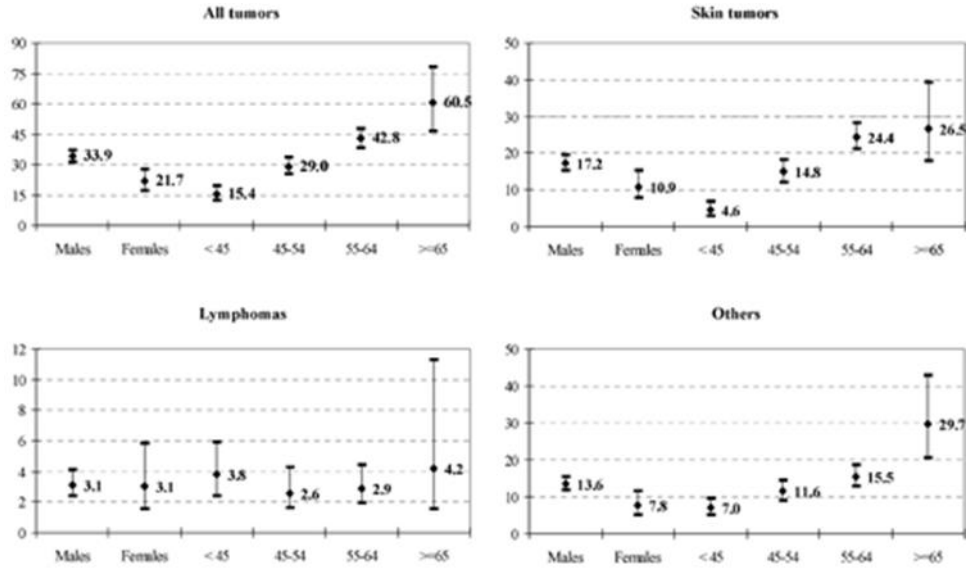
The duration of induction with ATG varied widely, between 1 and 20 days. The duration distribution peaked at 3 days (received by 61.6% of ATG-treated patients), 7 days (10.6%), 10 days (3.3%), 13 days (3.0%), 16 days (2.4%) and 20 days (0.9%), with the first peak (1–5 days) accounting for 73.1% of patients, the second (6–8 days) for 13.0%, the third (9–11 days) for 4.5%, the fourth (12–14 days) for 4.6%, the fifth (15–17 days) for 2.7% and the sixth (18–20 days) for 1.8%. Similarly, the duration of OKT3 treatment ranged from 1 to 30 days, with peaks between 1 and 3 days (10.6% of OKT3-treated patients, 8.1% receiving 3 days' treatment), between 4 and 5 days (19.2%, 12.4% receiving 5 days), between 6 and 8 days (44.3%, 35.4% receiving 7 days), between 9 and 11 days (2.4%, 1.2% receiving 10 days) and between 12 and 30 days (23.6%, 23.1% receiving 14 days).

Acyclovir was administered to 1369 patients (40.3%) during the first 3 months post-HT, ganciclovir to 1017 (30%) during the first month, and either acyclovir or ganciclovir (or both) to 1815 (53.5%).

A total of 639 tumors developed in 490 patients. Half (324, 50.7%) were skin cancers, 62 (9.7%) were lymphomas and 253 (39.6%) were noncutaneous solid cancers other than lymphoma. Apart from the skin, the most common locations were the lung (64 tumors, 10.1%), prostate gland (25, 3.9%), liver (18, 2.8%), bladder (18, 2.8%), colon (15, 2.4%) and stomach (14, 2.2%); no other location accounted for more than 2% of all tumors. The most common histopathological types or conditions were squamous cell carcinoma (207 tumors, 33.5%), adenocarcinoma (97, 15.7%), basal cell carcinoma (92, 14.9%), lymphoproliferative disorder (62, 10%), other carcinomas (38, 6.2%), transitional cell carcinoma (15, 2.5%), metastatic adenocarcinoma (11, 1.8%), Kaposi's sarcoma (10, 1.6%), metastatic squamous cell carcinoma (9, 1.5%) and melanoma (9, 1.5%); no other histological type accounted for more than 1.5% of all tumors.

The overall incidence of neoplasia per 1000 person-years was 18.7 one year after HT (95% CI 14.6–24.0), 22.7 after 5 years (95% CI 20.2–25.4) and 30.4 after 10 years (95% CI 28–33) (Table 2). The incidence of skin cancer and other tumors increased with time after HT, but not that of lymphoma (Table 2).

For skin cancer and other nonlymphoma tumors, the incidence per 1000 person-years was higher among men than among women (17.2 vs. 10.9, p = 0.012 for skin cancer; 13.6 vs. 7.8, p = 0.011 for others; see Figure 1). The incidence of lymphoma was 3.1 for both men and women (p = 0.948).




| | Males | Females | < 45 | 45-54 | 55-64 | >=65 |
|---|---|---|---|---|---|---|
| Person-years | 16,940.41 | 2,944.67 | 5,258.96 | 6,136.03 | 7,547.42 | 942.67 |
| All tumors | 575 | 64 | 81 | 178 | 323 | 57 |
| Skin tumors | 292 | 32 | 24 | 91 | 184 | 25 |
| Lymphomas | 53 | 9 | 20 | 16 | 22 | 4 |
| Others | 230 | 23 | 37 | 71 | 117 | 28 |

**Figure 1**. Incidence of tumors, for each sex and age group.**Estimated incidence per 1000 person-years; error bars show 95% confidence intervals.

For skin cancer, incidence per 1000 person-years increased from 4.6 among patients aged <45 years at HT to 26.5 among patients aged ≥65 years (Figure 1), with relative risks of 3.3 (95% CI 2.1–5.1, p < 0.0001) for 45–54-year-olds, 5.3 (3.5–8.2, p < 0.0001) for 55–64-year-olds and 5.8 (3.3–10.2, p < 0.0001) among patients aged ≥65 years, relative to under-45s (Table 3). Similarly, for other nonlymphoma tumors, incidence increased from 7.0 in the youngest age group to 29.7 in the oldest, with relative risks of 1.6 (95% CI 1.1–2.4, p = 0.013), 2.2 (1.5–3.2, p < 0.0001) and 4.2 (2.6–6.9, p < 0.0001) relative to under-45s. There were no significant differences among the four age groups as regards the incidence of lymphoma.

Pre-HT smoking was a risk factor for noncutaneous tumors other than lymphoma (RR 1.9, 95% CI 1.5–2.5; p < 0.0001), but not for either skin cancer or lymphoma (Table 3). HT era did not affect the risk of lymphoma or other noncutaneous cancers, but for skin cancer risk was significantly less in the IL2R-blocker era than in the period 1984–1997 (RR = 0.3, 95% CI 0.2–0.6; p = 0.0001), and the reduction in risk in the period 1998–2000 (RR = 0.8, 95% CI 0.6–1.0) also neared statistical significance (p = 0.08).

**Table 2**. Incidence of tumors

| | Person-years | All tumors | | Skin cancer | | Lymphomas | | Others | |
|---|---|---|---|---|---|---|---|---|---|
| | | Tumors | IR[1] (95% CI[2]) | Tumors | IR[1] (95% CI[2]) | Tumors | IR[1] (95% CI[2]) | Tumors | IR[1] (95% CI[2]) |
| Overall | 19 885.1 | 639 | 32.1 (29.7–34.7) | 324 | 16.3 (14.6–18.2) | 62 | 3.1 (2.4–4) | 253 | 12.7 (11.3–14.4) |
| Cumulative at: | | | | | | | | | |
| 3 months | 847.3 | 11 | 13 (7.2–23.4) | 2 | 2.4 (0.6–9.4) | 3 | 3.5 (1.1–11) | 6 | 7.1 (3.2–15.8) |
| 6 months | 1676.1 | 28 | 16.7 (11.5–24.2) | 6 | 3.6 (1.6–8) | 7 | 4.2 (2–8.8) | 15 | 9 (5.4–14.8) |
| 1 year | 3262.6 | 61 | 18.7 (14.6–24) | 17 | 5.2 (3.2–8.4) | 15 | 4.6 (2.8–7.6) | 29 | 8.9 (6.2–12.8) |
| 2 years | 6161.7 | 126 | 20.5 (17.2–24.4) | 44 | 7.1 (5.3–9.6) | 20 | 3.3 (2.1–5) | 62 | 10.1 (7.8–12.9) |
| 3 years | 8679.8 | 172 | 19.8 (17.1–23) | 64 | 7.4 (5.8–9.4) | 22 | 2.5 (1.7–3.9) | 86 | 9.9 (8–12.2) |
| 4 years | 10 888.3 | 226 | 20.8 (18.2–23.7) | 86 | 7.9 (6.4–9.8) | 28 | 2.6 (1.8–3.7) | 112 | 10.3 (8.6–12.4) |
| 5 years | 12 789.0 | 290 | 22.7 (20.2–25.4) | 118 | 9.2 (7.7–11.1) | 35 | 2.7 (2–3.8) | 137 | 10.7 (9.1–12.7) |
| 10 years | 18 308.1 | 556 | 30.4 (28–33) | 270 | 14.8 (13.1–16.6) | 55 | 3 (2.3–3.9) | 231 | 12.6 (11.1–14.4) |

[1]Incidence per 1000 person-years.
[2]Confidence interval.

**Table 3**. Relative risks (RR) of skin cancer, lymphoma and other tumors associated with various factors (univariate analyses)

| | Skin cancer | | Lymphomas | | Others | |
|---|---|---|---|---|---|---|
| | RR[1] (95% CI[2]) | p Value | RR[1] (95% CI[2]) | p Value | RR[1] (95% CI[2]) | p Value |
| Sex | | | | | | |
| Male | 1.6 (1.1–2.3) | 0.0124 | 1 (0.5–2.1) | 0.9483 | 1.7 (1.1–2.7) | 0.0105 |
| Female | 1.00 | – | 1.00 | – | 1.00 | – |
| Age group | | | | | | |
| <45 years | 1.00 | – | 1.00 | – | 1.00 | – |
| 45–54 years | 3.3 (2.1–5.1) | <0.0001 | 0.7 (0.4–1.3) | 0.2577 | 1.6 (1.1–2.4) | 0.0132 |
| 55–64 years | 5.3 (3.5–8.2) | <0.0001 | 0.8 (0.4–1.4) | 0.3879 | 2.2 (1.5–3.2) | <0.0001 |
| > = 65 years | 5.8 (3.3–10.2) | <0.0001 | 1.1 (0.4–3.3) | 0.8414 | 4.2 (2.6–6.9) | <0.0001 |
| Pre-HT smoking | 1.1 (0.9–1.4) | 0.2561 | 1 (0.6–1.7) | 0.9324 | 1.9 (1.5–2.5) | <0.0001 |
| HT era | | | | | | |
| 1984–1997 | 1.00 | – | 1.00 | – | 1.00 | – |
| 1998–2000 | 0.8 (0.6–1) | 0.0789 | 0.9 (0.5–1.8) | 0.8667 | 1 (0.7–1.3) | 0.8871 |
| 2001–2003 | 0.3 (0.2–0.6) | 0.0001 | 0.7 (0.3–2) | 0.5042 | 1 (0.6–1.5) | 0.9399 |
| MMF (Yes/No) | 0.5 (0.3–0.7) | 0.0003 | 0.8 (0.4–1.8) | 0.6535 | 1 (0.7–1.4) | 0.9699 |
| Tacrolimus (Yes/No) | 0.3 (0.1–0.8) | 0.0105 | 0.8 (0.2–3.2) | 0.7298 | 1.0 (0.5–1.9) | 0.9601 |
| Induction therapy[3] | 2.1 (1.7–2.8) | <0.0001 | 1.5 (0.9–2.5) | 0.1497 | 2.2 (1.6–3) | <0.0001 |
| OKT3[3] | 2.5 (1.9–3.3) | <0.0001 | 1.2 (0.7–2.2) | 0.5600 | 2.1 (1.5–2.9) | <0.0001 |
| ATG[3] | 1.6 (1.1–2.2) | 0.0113 | 2.4 (1.3–4.5) | 0.0044 | 2.5 (1.8–3.6) | <0.0001 |
| Basiliximab[3] | 0.7 (0.2–2.4) | 0.6187 | 0.00 | 0.3163 | 1.6 (0.7–4.1) | 0.2891 |
| Daclizumab[3] | 0.00 | 0.1443 | 0.00 | 0.4654 | 1.8 (0.6–5.9) | 0.2938 |
| Antiviral prophylaxis | | | | | | |
| Acyclovir[4] | 1.2 (0.9–1.4) | 0.1828 | 0.6 (0.3–1) | 0.0500 | 1.1 (0.8–1.4) | 0.5341 |
| Ganciclovir[5] | 1.5 (1.2–1.9) | 0.0007 | 0.9 (0.5–1.6) | 0.6795 | 0.8 (0.6–1.1) | 0.1971 |
| Acyclovir or Ganciclovir[6] | 1.9 (1.5–2.4) | <0.0001 | 0.7 (0.4–1.2) | 0.1921 | 1.1 (0.9–1.4) | 0.4545 |

[1]RR: relative risk.
[2]CI: confidence interval.
[3]Relative to no induction therapy.
[4]Relative to no acyclovir.
[5]Relative to no ganciclovir.
[6]Relative to 'neither acyclovir nor ganciclovir'.

In keeping with the observed influence of HT era, in univariate analyses (Table 3) the use of MMF and the use of tacrolimus (both in the first 3 months after HT, and regardless of any later use) were both associated with a lower incidence of skin cancer (RR = 0.5 (95% CI 0.3–0.7), p = 0.0003 for MMF; RR = 0.3 (95%CI 0.1–0.8), p = 0.01 for tacrolimus). However, neither MMF nor tacrolimus showed a similar relationship with the incidence of lymphoma or other tumors. Multivariate analysis showed the influence of MMF on skin cancer to be independent of the effects of sex, age group, pre-HT smoking, use of tacrolimus in the first 3 months, induction treatment and antiviral treatment (RR = 0.38, 95% CI 0.25–0.58), but an analogous analysis showed that the decrease in the incidence of skin cancer that was associated with tacrolimus treatment in the first 3 months was no longer statistically significant when corrected for the effects of sex, age group, pre-HT smoking, use of MMF in the first 3 months, induction treatment and antiviral treatment (RR = 0.5, 95% CI 0.18–1.36).

In univariate analyses, antiviral prophylaxis with acyclovir was associated with decreased risk of lymphoma (RR = 0.6, 95% CI 0.3–1.0; p = 0.05), but treatment with ganciclovir, or with either ganciclovir or acyclovir, was associated with increased risk of skin cancer (Table 3).

Induction with IL2R blockers (basiliximab or daclizumab) did not significantly influence the risk of any type of tumor (Table 3). By contrast, induction therapy in general was a risk factor for both skin cancer (RR = 2.14, 95% CI 1.7–2.8; p < 0.0001) and other nonlymphoma cancers (RR = 2.2, 95% CI 1.6–3.0; p < 0.0001), and in both cases this result is attributable to the effects of OKT3 and ATG (Table 3).

In the univariate analyses, the influence of ATG differed from that of OKT3 in that ATG was associated not only with increased risk of skin cancer and other nonlymphoma cancers, but also with increased risk of lymphoma (RR = 2.4, 95% CI 1.3–4.5; p = 0.004). However, when age group, sex, pre-HT smoking and immunosuppression in the first 3 months with MMF and/or tacrolimus were controlled for while estimating the association of tumors with OKT3, ATG or induction in general for each of the four antiviral prophylaxis groups that were distinguished (see Methods), then increased risk of lymphoma was associated with both ATG and OKT3 among patients who were not given acyclovir {RR = 3.6 (95% CI 1.6–7.9) for ATG, 2.2 (1.4–7.0) for OKT3, 2.8 (1.5–5.4) for induction in general} and among patients

given neither acyclovir nor ganciclovir {RR = 3.7 (95% CI 1.6–8.3) for ATG, 2.7 (1–7.4) for OKT3, 3.2 (1.6–6.6) for induction in general}, but was not associated with either agent among patients given acyclovir or patients given either acyclovir or ganciclovir (Figure 2).

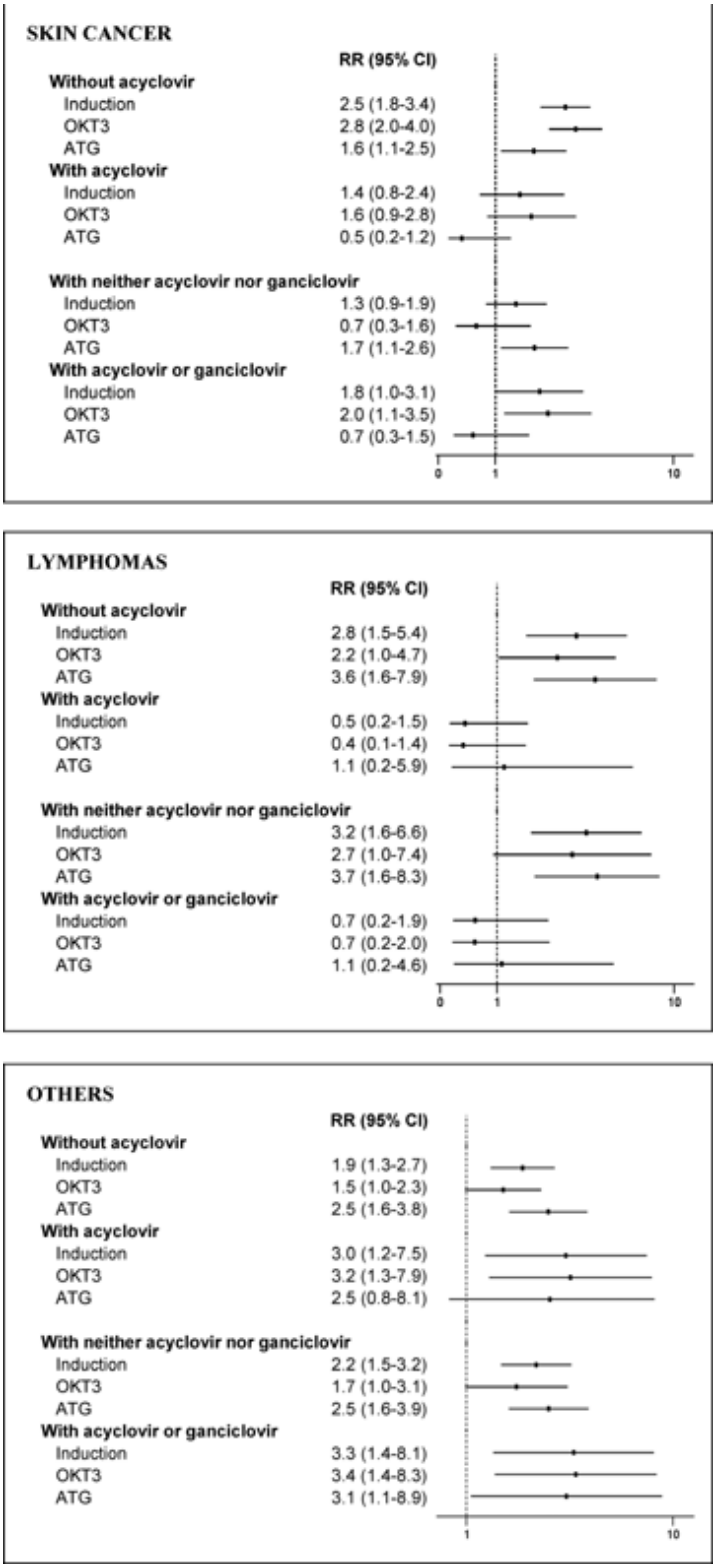
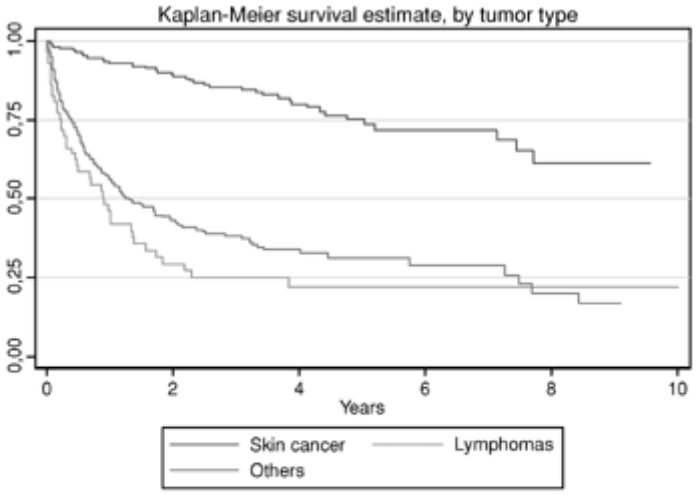



**Figure 2**. Effect of induction therapies on the risk of post-HT tumors for patients who were and were not given antiviral prophylaxis with acyclovir, and for patients who were and were not given antiviral prophylaxis with acyclovir or ganciclovir, after adjustment for sex, age group, pre-HT smoking and MMF or tacrolimus in the first 3 months.'ATG' includes both equine and rabbit ATG.

Similar analyses for skin cancer afforded strictly parallel results only as regards the influence of acyclovir: among patients who did not receive acyclovir, both OKT3 and ATG were associated with increased risk {RR = 1.6 (95% CI 1.1–2.5) for ATG, 2.8 (2.0–4.0) for OKT3 and 2.5 (1.8–3.4) for induction in general}, whereas neither OKT3 nor ATG was associated with significantly increased risk among patients who did receive acyclovir. Among patients who received neither acyclovir nor ganciclovir, ATG was associated with increased risk (RR = 1.7, 95% CI = 1.1–2.6), but not OKT3; while among patients who did receive either acyclovir or ganciclovir, OKT3 was associated with increased risk (RR = 2.0, 95% CI 1.1–3.5), but not ATG.

With regard to noncutaneous tumors other than lymphoma, increased risk was associated with OKT3 but not ATG if acyclovir treatment was given, but with both OKT3 and ATG if acyclovir was not given. Increased risk was also associated with both OKT3 and ATG in both the groups defined without regard to the identity of the antiviral prophylactic.

Figure 3 shows Kaplan-Meier curves for survival after presentation of a first post-HT tumor, distinguishing among skin cancers, lymphomas and other tumors. In a total follow-up time of 1220.7 person-years, 213 deaths occurred. The actuarial survival rates 1, 5 and 10 years after tumor diagnosis were 93%, 74% and 61%, respectively, for skin cancer; 60%, 20% and 20% for lymphoma and 72%, 32% and 17% for other tumors. The prognosis for skin tumors was thus considerably better than for lymphomas or other tumors (log-rank test $p < 0.0001$).




| | | | | Follow-up time (years) | | | |
|---|---|---|---|---|---|---|---|
| | Tumors | Deaths | Person-years | P25 | P50 | P75 | Mean |
| All tumors | 482 | 213 | 1,241.0 | 0.6 | 1.7 | 3.9 | 2.5 |
| Skin tumors | 212 | 41 | 746.3 | 1.3 | 3.0 | 5.0 | 3.5 |
| Lymphomas | 57 | 40 | 107.1 | 0.2 | 0.7 | 2.0 | 1.7 |
| Others | 213 | 132 | 387.6 | 0.3 | 0.9 | 2.5 | 1.9 |

**Figure 3**. Survival following diagnosis of first tumor.

## Discussion

As far as we know, this has been the only study of post-HT malignancy to have followed up all HT cases in a population exceeding 38 million over a 20-year period, gathering comprehensive malignancy data throughout follow-up.

The general demographic characteristics of Spanish HT patients have been similar to those of patients included in the ISHLT Registry, with a mean age of 51.4 years (cf. 50.6 years among recent ISHLT patients (2)) and a male:female ratio of about 4:1 (this paper, 85:15; ISHLT, 77:23).

In terms of the percentage of patients developing neoplasia, the overall incidence of neoplasia among Spanish HT patients also seems to have been similar to that of ISHLT patients: in this study, in which median post-HT follow-up time was 5.2 years, overall incidence was 14.4%, a figure intermediate between the 15.6% reported among 5-year survivors in the 2006 ISHLT Registry report (2) and the 14.1% observed within the first 5 years post-HT in O'Neill et al.'s study (8) of a 3895-member subset of that

Registry (although O'Neill et al.'s study only analyzed data for about 50% of its potential subjects, no data on malignancy having been reported at 1-year follow-up for the others). Our patients were also similar to those studied by O'Neill et al. (8) as regards the distribution of neoplasias among skin cancers (about 50%), lymphomas (about 10%) and others.

With regard to the evolution of incidence with time post-HT, lymphomas behaved differently from skin cancers and other nonlymphoma neoplasias. Whereas the incidence of the latter types increased with time, especially in the case of skin cancers, that of lymphomas did not. The incidence of lymphomas per 1000 person-years during successive 1-year periods was greatest during the first year post-HT {as in Opelz et al.'s analysis of the CTS data base (9)}, but then fell and eventually leveled off at about 3.8 (as can be calculated from the data shown in Table 2), whereas in Opelz et al.'s study incidence continued to rise for at least 5 years.

As in O'Neill et al.'s study (8), in this study the overall incidence of neoplasia increased with age and was about 1.6 times greater among men than among women. However, the incidence of lymphomas did not share the age- and sex-dependence of skin cancer and other neoplasias: women had lymphomas as often as men, and although the observed incidence of lymphoma did increase very slightly with age, this increase was far from being statistically significant. This lack of age dependence is in keeping with the results of Opelz et al. (9), who in their CTS-based study of posttransplant lymphoma found that the 5-year risk of non-Hodgkin lymphoma decreased with increasing age relative to that of a simulated general population with the same demographic characteristics as their transplant population, falling from 130 for 21–30-year-olds to 16.4 for over-60s.

Whereas age and sex are unavoidable risk factors, induction therapy, if it is a risk factor, is in principle an avoidable one. Induction agents did not emerge as risk factors in O'Neill et al.'s study (8), and the fact that the proportion of our patients given some kind of induction therapy, 61%, was about 1.3 times the ISHLT average for the period 1996–2004 (2) and about 1.5 times the proportion in O'Neill et al.'s study (37%) does not appear to have led to a greater incidence of malignancy. It is necessary, however, to distinguish among different induction agents. In the study that first drew attention specifically to the dangers of OKT3, this agent was an independent risk factor for PTLD but equine ATG was not (15). A similar result was found by Opelz et al. among patients who underwent HT before 1990 (9); and in a small (207-patient) study by El-Hamamsy, rabbit ATG did not increase the incidence of neoplasia, although it was associated with earlier development and earlier death (12). The perception of higher risk of PTLD with OKT3 induction led to a fall in the use of OKT3 during the 1990s, even before the introduction of IL2R-blockers (2,9). However, in this study, induction with OKT3 and induction with ATG were both risk factors for skin cancer and other nonlymphoma neoplasias, and the only induction agent increasing the risk of lymphoma was ATG (Table 3). OKT3 did not increase the risk of lymphoma, and IL2R-blockers did not increase the risk of any type of neoplasia.

As regards OKT3, the difference between our results and Swinnen et al.'s is probably attributable to the use of different OKT3 dosages. Swinnen et al.'s OKT3 induction regimen was 5 mg daily for 14 days, whereas the mean duration of OKT3 induction in this study was 7.8 days (SD 3.9 days). A sharp post-1990 fall in the incidence of lymphoma among OKT3-induced patients in the CTS data base has similarly been attributed to probable reductions in dosage and treatment duration (9). Why ATG was associated with increased risk among Spanish patients is unclear.

Drugs used for immunosuppression are difficult to evaluate on the basis of registry data because of the multiplicity of drug combinations and because the immunosuppressive regimens of patients not involved in controlled trials are liable to changes inspired by the patient's response or by the reported advantages of new immunosuppressors. However, the SPHTTR data showed that the use of MMF for the institution of immunosuppression during the first 3 months after HT is associated with a lower incidence of skin cancer than azathioprine, although MMF was not similarly beneficial with regard to the incidence of lymphomas or other tumors. That an independent beneficial influence on skin cancer was shown by MMF but not tacrolimus is in keeping with O'Neill et al.'s finding that among patients maintained on a calcineurin inhibitor and an anti-metabolite the use of MMF rather than azathioprine was an independent predictor of reduced risk of malignancy within 5 years of HT but the use of tacrolimus rather than cyclosporine was not, even though univariate analyses indicated both MMF and tacrolimus to be beneficial (8).

Since the early 1990s, antiviral agents have in many centers been administered to transplant patients prophylactically during the first 3 months in order to reduce the risk of herpesvirus disease, especially CMV disease. For CMV, prophylaxis appears to be successful (18). The question arises whether it also reduces the incidence of virus-related tumors. Prophylaxis with ganciclovir has been reported to reduce the risk of PTLD for kidney transplant patients (19). In this study we found that prophylaxis with ganciclovir in the univariate analyses was associated with increased risk of skin cancers. Although ganciclovir has been reported to cause tumors in laboratory animals, our observation was unexpected and merits further investigation; that it might have been due to the ‘no ganciclovir’ group including patients

given acyclovir would seem to be ruled out by the fact that patients given either ganciclovir or acyclovir had a higher risk of skin cancer than those given neither. Acyclovir roughly halved the risk of post-HT lymphoma, and this finding is in keeping with the overall incidence of lymphoma in this study, 3.1 per 1000 person-years, having been rather less than half the 6.9 per 1000 person-years found among heart and/or lung transplantation patients in a 15-year single-center study in Melbourne, Australia, where most patients did not receive prophylactic antiviral drugs (10). Furthermore, whereas both OKT3 and ATG were associated with increased risk of all three types of neoplasia among patients who did not receive acyclovir, among patients who did receive acyclovir, induction therapy only increased the risk of noncutaneous, nonlymphoma neoplasias, and only when the induction agent was OKT3.

On the basis of the SPHTTR data, the prognosis for post-HT skin cancer is considerably more favorable than for other post-HT neoplasias, with thrice as many patients surviving for 10 years or more. The 1-year survival rate among post-HT lymphoma patients in Spain has been about the same as in Opelz et al.'s study (9), 50%, but the medium-term survival rate has been somewhat lower.

In conclusion, the incidence of post-HT neoplasias since the initiation of HTs in Spain has been about 19 per 1000 person-years during the first year post-HT and has increased with time post-HT thereafter. About 50% of post-HT tumors have been cutaneous, and only 10% lymphomatous; cutaneous tumors have had much the best prognosis. Induction therapy other than with IL2R-blockers has in general significantly increased the risk of neoplasia except when acyclovir (or in the case of lymphomas, ganciclovir) has been administered prophylactically during the first 3 months post-HT. In particular, prophylactic administration of acyclovir roughly halved the risk of lymphoma, regardless of other therapies.

The conclusions that can be drawn from this study are limited by the SPHTTR's almost complete lack of serological data other than for CMV. This has prevented investigation of how the observed relationships among the use of antiviral prophylaxis, induction treatment and the incidence of neoplasias may have depended on the serological status of patient and/or donor with regard to the viruses now known or suspected to be associated with certain posttransplant neoplasias. Additionally, it is too soon for it to have been possible to use the Registry to evaluate the effects of immunosuppressors of the recently introduced sirolimus family, the mammalian target-of-rapamycin inhibitors (mTORs), which offer great promise for reduction of the risk of post-HT neoplasia (20).

The results on lymphomas reported in this article were presented at the 2007 Annual Meeting of the ISHLT held in San Francisco, and has been published in the Journal of Heart and Lung Transplantation (21). They are included here for completeness and to facilitate comparison with the results for other tumors.

**Appendix**

The following investigators also contribute to the Spanish Post-Heart Transplant Tumor Registry: Maria J Paniagua and Jose A Rodriguez (Complejo Hospitalario Universitario Juan Canalejo, La Coruña); Javier Segovia and Manuel Gomez-Bueno (Clinica Puerta de Hierro, Madrid); Monica Fernandez-Valls and Francisco Gonzalez-Vichez (Hospital Universitario Marqués de Valdecilla, Santander); Luis Martinez-Dolz (Hospital Universitario La Fe, Valencia); Carmen Segura Saint-Gerons (Hospital Universitario Reina Sofia, Córdoba); Sonia Mirabet and Marta Camprecios (Hospital de la Santa Creu i San Pau, Barcelona); Miguel Angel Gómez-Sanchez and Pilar Escribano (Hospital Universitario 12de Octubre, Madrid); Jesús Palomo (Hospital General Universitario Gregorio Marañón, Madrid); Josep Roca (Hospital Universitario de Bellvitche, Barcelona); Matias Ubilla (Clínica Universitaria de Navarra, Pamplona); Félix Perez-Villa (Hospital Clinic i Provincial, Barcelona); Maria Martin-Fernández and Jose L. Rodriguez-Lambert (Hospital Universitario Central de Asturias, Oviedo); Iris P. Garrido (Hospital Universitario Virgen de la Arrixaca, Murcia); Maria Luisa Sanz-Julve and Teresa Blasco (Hospital Universitario Miguel Server, Zaragoza) and Luis de la Fuente-Galán and Javier López-Diaz (Hospital Clinico Universitario, Valladolid).

**Acknowledgments**

We are grateful to the researchers and staff of all the Spanish heart transplant centers that contributed data to this study; to the SPHTTR's coordinator, Zulaika Grille; to Soly Santiago for statistical analyses, tables and figures; to Francisco Arnal for advice on pathology and to Ian-Charles Coleman for helpful criticism and for the English version of this article.

This study was partially supported by an unrestricted grant from Astellas Pharma. Also, several centers and researchers participating in this study are members of the cardiovascular research network RECAVA, which is supported by the Spanish Ministry of Health and Consumer Affairs through the Instituto de Salud Carlos III.

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