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# *Transplantation and tumors*

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## THE PROBLEM OF ORGAN DONORS WITH A HISTORY OF TUMORS

The publication two years ago by Mackie et al. of a case of melanoma transferred during transplantation from a donor who was apparently tumor-free for the last 16 years showed the complexity of evaluating a history of tumors in donors, especially when the age of these donors, and hence the associated multiple pathologies, has tremendously increased in recent years[1]. Both the UNOS Registry and the Danish Cancer Registry suggest that this transfer of tumors through the graft is extremely low, less than 2 out of a thousand[2-4], although the mortality associated to these is quite considerable. Evidence of transferal has been published in cases of melanoma, choriocarcinoma, pancreatic adenocarcinoma, lymphoma, and lung, kidney, breast or colon carcinomas[5-11].

Due to the shortage of organs, donors with non-metastatic skin carcinomas, *in situ* carcinoma of the uterine cervix, central nervous system tumors (excluding cases of glioblastoma multiforme or medulloblastoma, existence of intracardiac defects, craniotomy or donors treated with systemic chemotherapy or radiotherapy) or low risk renal cancers (size less than 4 cm, free margins and Fuhrman histological grading I-II) are often times considered suitable donors[12-16]. The recommendations of Feng et al. for the use of donors with a history of breast or colon cancer who have been disease-free for a suitable amount of time to be a donor candidate are even more controversial[3].

Different strategies have been proposed to minimize the risk of tumor transfer[4], and recently in September 2005, the National Transplant Organization suggested criteria for preventing the transfer of neoplastic diseases[15]. All of these strategies are debatable and not always logistically easy to carry out to practice in cases of urgently obtaining the organs. They include measuring blood or urine bHCG (choriocarcinoma), PSA (prostate adenocarcinoma) or electrophoretic spectrum (monoclonal gammopathies), tomographies, thorough inspection of lymph nodes, chest or abdominal organs with an immediate biopsy when obtaining the organs, or performing routine autopsy[17,18].

Managing a patient with a tumor originating from the donor is fairly complex. In the case of renal transplant recipients, transplantectomy and the discontinuation of immunosuppression with or without tumor-specific therapy have been recommended, although with some exceptions. In the case of donors with renal cancer and given the activity of sirolimus in this type of tumors, an immunosuppression based on this drug could be an alternative[19,20]. When a patient with a tumor originating from the donor is the recipient of a non-renal organ, the situation is even more dramatic, and urgent re-transplants have had to be performed.

## THE PROBLEM OF TRANSPLANT CANDIDATES WITH A HISTORY OF TUMORS

As a general approach, candidates for renal transplantation with previous malignancy history should remain some tumor-free before entering the waiting list[21]. When considering these type of patients as transplant candidates, it is important to know the risk of post-transplant tumor relapse. Three relapse risk categories have been established through the UNOS Registry[3]: a) low risk including incidental renal carcinoma (discovered in bilateral nephrectomy before or at the same time as the transplant), uterine, testicular, cervical or thyroidal cancer; b) moderate risk including lymphoma, Wilms' tumor, prostate and colon cancer; c) high risk including breast cancer, symptomatic renal carcinoma, bladder carcinoma, sarcoma and skin cancer. Thus, the required time to elapse tumor-free will depend on the type of tumor.

Otley et al. recently raised the issue of whether patients with a history of skin cancer should be ac-

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cepted as transplant candidates[22]. In their opinion metastatic forms of skin squamous or basal cell or Merkel carcinomas and melanomas with stages ≥ 2 should clearly be excluded.

In relation to PTLD, re-transplant after complete lasting remission is possible, although it is difficult to recommend the period for safely doing so[23].

The IPITTR *(Israel Penn International Transplant Tumor Registry)* has recently reported the results of 90 patients with pre-transplant prostate cancer who received a graft with a median of almost two years after diagnosis. Tumor relapse was observed in 17% of patients and tumor-related mortality was 8% after 20 months of follow-up[24]. These figures must be balanced with mortality figures of waiting-list patients. A lot still needs to be learned about prognostic, histological, surgical or analytical (PSA) factors in order to customize decision making[25].

Some groups are transplanting these patients with sirolimus-based regimens. The University of Philadelphia group had used sirolimus from the beginning in 27 patients and observed no relapses after 3 years of follow-up[26]. However, heterogeneity of this group of tumors makes it difficult to establish firm conclusions.

## POST-TRANSPLANT TUMORS

Most information related to the incidence of post-transplant tumors are from retrospective multicenter registries, such as the Israel Penn International Transplant Tumor Registry (IPITTR) (formerly known as the Cincinnati Transplant Tumor Registry), the Australian-New Zealand Registry, the CTS (Collaborative Transplant Study) Registry or the US-RDS Registry.

Cardiovascular diseases and tumors are the two main causes of death with graft function in long-term follow-up of renal transplant patients. The Australian-New Zealand Registry even suggests that the second factor could be more prevalent that the first one[27]. Different factors could contribute to this, including an increase in the mean age of the recipients[28], the improvement in survival that has thus extended the observation period or the better treatment of the cardiovascular factors including the more frequent use of hypolipidemic agents[29].

Therefore the accumulated incidence of tumors can reach 20% after 10 years[30] and almost 30% after 20 years[28,31]. In some geographic locations such as Australia, the accumulated incidence can reach 65% after 20 years if skin cancers are included.

The rate of expected versus observed cancers varied in the different registries. The approximate results are provided in the table below:

| Type of tumor | Ratio compared to general population[28, 30, 32-35] |
|---|---|
| Non-melanoma skin cancer | 65-92 |
| Kaposi's sarcoma | 17-84 |
| Uterus | 30 |
| Penis | 17 |
| Kidney | 8-14 |
| Lymphoproliferative disease | 6-29 |
| Endocrine, including thyroids | 2-14 |
| Mouth | 4-11 |
| Melanoma | 3-7 |
| Vulvovaginal | 8-45 |
| Cervix | 6 |
| Total (excluding non-melanocytic skin) | 3 |

Viral and immunosuppressive infections influence the pathogeny of post-transplant tumors. In this sense, cyclosporin and tacrolimus seem to have an oncogenic role per se, through a mechanism in which TGF-b is involved[36,37]. mTOR inhibitors such as sirolimus or temsirolimus seem to have an anti-tumor effect by means of VEGF antagonism and angiogenesis, a blockage of the phosphatidylinositol 3-kinase pathway in tumors harboring mutations in the tumor suppressor gene PTEN, a reduction of cyclin D1 with a cell cycle arrest, reduced invasive phenotype by means of an increase in E-cadherin and an increase in apoptosis of at least the lymphomatous cells[38-40].

### Skin Carcinomas

Non-melanocytic skin tumors (squamous cell and basal cell) are the «de novo» tumors most frequently occurring after renal transplantation, and they represent about 90% of skin tumors in this population. In some geographic areas it is a very prevalent problem. In this sense, in Australia the accumulated incidence is 30% and 82% after 5 and 20 years, respectively[41]. Skin squamous cell carcinoma is the most frequent post-transplant carcinoma, occurring 65 to 250 times more frequently than in the general population. Basal cell carcinoma is 10 times more

frequent among transplant recipients than in the general population.

The onset risk factors are the elderly age of the recipient[42], male sex[42], the longer duration of pre-transplant dialysis time[43], the duration of post-transplant immunosuppression[41,42], skin phototype and different ethnic groups[44,45], the type of transplanted organ (more frequent in cardiac transplantation than in renal transplantation[46]), greater exposure to ultraviolet radiation[44,47], geographic location (higher to lower incidence reported in: Australia-New Zealand, Spain and the Mediterranean area, Holland and Northern Europe, and Japan)[41,42,47-51], and the presence of pre-malignant skin lesion such as warts or actinic keratosis. The Oxford group has found a relation between deteriorated renal function one year after the transplant and a higher incidence of skin tumors[42]. Certain genetic susceptibility is suggested by the association between the onset of non-melanocytic skin tumors and different polymorphisms in the interleukin-10 gene, glutathione transferase gene, the HLA system gene or the p53 gene[52-54]). Serotype 5 and 8 human papillomavirus infection plays an important pathogenic role[55].

The time of presentation after the transplant is inversely proportional to the age of the transplant: so the time of maximum risk is 6 years after the transplant for patients under 50 years of age, and 2 years for patients over that age[56]. The presentation is usually age-dependent: on the back of the hands and torso in young recipients and on the head in elderly recipients[57]. It is much more frequent that squamous cell carcinoma has an invasive phenotype than in the non-transplanted population[56], and most metastasis spread to regional nodes or to neighboring skin[58,59]. The presentation is often relapsing[35,60].

The relation between the immunosuppression received and skin tumors was already reported in 1971 when Walder et al. communicated a 14% increase in the incidence of tumors together with a reversal of the proportion between squamous and basal cell carcinomas. While the proportion is 5 to 1 in favor of basal cell carcinomas in the general population, it is 1.8 to 1 in favor of squamous cell carcinomas in transplant recipients[61]. A reduced number of CD4 lymphocytes has been related as a risk factor for skin tumors[62]. The contribution of cyclosporin to the development of post-transplant skin tumors has been indicated by British, French and Norwegian groups upon finding a greater incidence with triple immunosuppressive therapies based on cyclosporin, azathioprine and steroids than with dual therapies with azathioprine and steroids[34,43,63]. A randomized study with two doses of cyclosporin found a lower incidence in the group with less exposure[64]. There is less information related to tacrolimus, but according to Kasiske and Durando, patients with tacrolimus at the time they are released would have 35% fewer non-melanocytic skin tumors than when tacrolimus is not present upon release[65]. In relation to sirolimus, the joint analysis of two randomized trials showed that the combined use of sirolimus plus cyclosporin showed a lower incidence of skin tumors than the placebo group[66]. The Texas Group found a 2.4% incidence of skin tumors in its cohort treated with sirolimus-cyclosporin, which means an increase of only 1.5 times the incidence of the general population[67]. The results of a randomized five year trial also showed that when cyclosporin is suspended and the patients are maintained with sirolimus and steroids, the incidence of skin tumors is lower than in treatment with the three drugs[68].

The management of these non-melanocytic skin tumors has recently been described[60,69]. In cases of basal cell carcinoma or in cases of multiple squamous cell carcinoma, excision is recommended. In cases of high risk squamous cell carcinomas (located in the head, genitals or nail; diameter exceeding 2 cm; ulceration or fast growth) or in cases of local relapse, Mohs surgery is recommended. Oral retinoids could be useful for controlling the development of tumors in cases of premalignant lesions or as secondary prophylaxis, but tolerance to these drugs is often not optimal[70]. In relation to immunosuppression, the reduction thereof[71] or conversion of the patients to sirolimus has been suggested[72]. Metastatic forms have been treated with surgery or local-regional radiotherapy[59].

**Kaposi's Sarcoma**

The incidence of Kaposi's sarcoma is much greater than in the non-immunosuppressed population. It usually begins about a year after the transplant, predominantly in males. It entails skin, mucosal and visceral (glands, gastrointestinal tract or lung) lesions. Its pathogeny is related to a reactivation of type 8 herpes virus infection. Long-term survival depends on the degree of systemic involvement: one-year survival rates ranging from 90% for skin forms to 70% for visceral forms. It has traditionally been treated by means of reducing immunosuppression with or without different chemotherapy regimens including vinblastine, bleomycin, doxorubicin or others[73]. Several cases of successful treatments with conversion to sirolimus have recently been reported[74-81].

**Post-transplant Lymphoproliferative Disease (PTLD)**

The relative risk of post-transplant lymphoproliferative disease in relation to the general population is between 10 and 29 times higher[28,30,32,67,82].

PTLD is linked to a deficient cellular immune response against Epstein-Barr virus (EBV)[83]. The risk factors for developing PTLD include pediatric age, male sex[84], prior history of tumors, Caucasian race[84], EBV-seronegativity , donor-receiver CMV serological disparity[85], and the type of transplanted organ[82,86,87] (probably reflecting the immunosuppression intensity received going from higher to lower accumulated incidence in intestine, heart-lung, lung, heart, liver, pancreas and kidney). The importance of immunosuppression received was already reported with the emergence of cyclosporin and at the beginning of the 1990s with the use of OKT3 in cardiac transplantation[88,89]. Later experiences have indicated the higher risk with OKT3[82,90] or ATG[82,87]. However, the most recent regimens with ATG seem to be somewhat decreasing the incidence of lymphomas. Antibody inductions against the IL-2 receptor do not seem to imply a higher risk[82,91]. Mycophenolate mofetil seems to offer a lower risk of lymphomas than azathioprine[91,92], and tacrolimus somewhat more than cyclosporin[82,87,90,93]. In relation to sirolimus, data in murine models suggests an EBV+ lymphoma growth inhibitor effect[94], and Kahan et al. have found that the incidence of PTLD with the combination of sirolimus and cyclosporin is lower than that historically reported with other regimens[67]. Treatments with acyclovir or ganciclovir are other factors that would reduce the risk of PTLD onset[95].

Symptoms of early onset, in the first year of the transplant, and of later onset have been described, early onset tending to show greater transplanted organ involvement, and more CD20 and EBV-positive cases[96]. PTLD differs from other lymphomatous syndromes in the general population in that high degrees of histological malignancy, of extranodal involvement and of more aggressive courses are more frequent. Two different histological forms are distinguished: a monomorphic form (B or T cell lymphoma, which generally has characteristics of large cell diffuse lymphoma) and a polymorphic form that is more difficult to characterize and requires conducting cloning assessment techniques[97].

Median survival is somewhat less than 3 years[98]. In addition to the classic adverse prognostic factors such as age, advanced stage, poor general condition, high LDH levels or the presence of an extranodal disease[99], experience at Bellvitge Hospital and the Mayo Clinic suggests that the lymphomatous involvement of the transplanted organ confers an especially poor prognosis[98,100]. IPITTR data also suggests that the central nervous system involvement confers a very negative prognosis[101].

Managing these syndromes has included approaches such as surgery to eradicate localized forms or transplantectomy of the organ involved[102], reducing immunosuppression to a minimum[103-105], the use of standard chemotherapy regimens[106,107], the use of interferon[108], and more recently the use of rituximab[109-113]. Treatments have been tested experimentally by means of infusing EBV-specific cytotoxic lymphocytes[114]. Monitoring EBV viral copies does not seem useful to predict the development of PTLD[89]. Sirolimus conversions have been conducted after diagnosing PTLD. Sirolimus-based immunosuppression thus allows transplanted organ maintenance associated to various strategies including chemotherapy, rituximab or even intensification with autologous hematopoietic stem-cell transplantation[115-128].

**Other Non-skin Solid Tumors**

Although transplantation is clearly associated to PTLD and skin tumors, the relation between transplantation and other tumors has been more controversial, although according to Kasiske et al., incidence would be higher with respect to the general population in all types of tumors[32]. Different data has recently indicated that these results could be different with two immunosuppressive agents: mycophenolate mofetil and sirolimus. In this sense a joint analysis of the observational CTS registry and the UNOS Registry would suggest a certain non-significant trend towards fewer tumors in patients treated with mycophenolate, together with a significant increase of the time it takes the tumor to develop[92]. Data showing favorable results with sirolimus are from registries with a large number of patients[67,129] and from several randomized clinical trials[66,68]. The retrospective UNOS Registry with over 33,000 patients concluded that maintenance immunosuppression based on mTOR inhibitors with or without calcineurin inhibitors is significantly associated to a lower number of any «de novo» tumor and to a lower number of non-skin «de novo» tumors than maintenance with calcineurin inhibitors alone[129]. The single-center, retrospective analysis of Dr. Kahan's group of 1008 recipients treated with sirolimus – cyclosporin with or without steroids and monitored for a median time of 5 years, found an incidence of tumors, especially skin tumors, and PTLD that were lower

than their historical series[67]. Campistol et al. have recently reported the results of a randomized 5-year trial showing that the incidence of non-skin tumors is significantly lower when cyclosporin is discontinued and sirolimus and steroids are maintained than if the patient is maintained with the three drugs (4% versus 9.6%)[68]. The antitumor role of mTOR inhibitors is emphasized by the fact that temsirolimus (a sirolimus derivative) is currently being developed for treating breast cancer, renal cancer and mantle cell lymphoma[20,130,131].

Management for all these types of tumors is tremendously heterogeneous. With regards to immunosuppression, several groups are conducting sirolimus conversions which allow maintaining suitable renal function and a certain associated antitumor effect[132]. Given the wound healing problems reported with this drug, it seems reasonable to delay starting with it until after surgery, if this is even required.

The European Guidelines for transplantation follow-up have suggested tumor screening policies in order to enable early intervention[133-137]. The following table is a summary of these recommendations:

a) Promoting healthy-living habits including abstaining from smoking, avoiding exposure to ultraviolet rays and the use of protective sun screens.
b) Early diagnosis of tumor complications by means of:

- History and physical examination to detect PTLD (every 3 months during the first year and yearly after that), specially in EBV negative recipients.
- Consult a dermatologist (every 6 months in high-risk patients, yearly for the rest)
- Ultrasonography or abdominal tomography of native kidneys (yearly)
- Gynecological examination (cytology and ultrasonography) (yearly)
- Mammography (yearly or every 2 years) in > 50 years
- Measuring PSA and rectal exam in males > 50 years (yearly)
- Fecal occult blood (in > 50 years, yearly)
- α-fetoprotein levels (in HBV or HCV positive patients)
- Cytoscope (in cases of hematuria)

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