Corneal Transplantations From Donors With Cancer

Antonio López-Navidad,1,5 Nuria Soler,2 Francisco Caballero,1 Enrique Lerma,3 and Óscar Gris4

Background. Acceptance criteria for corneal donation in some eye banks include cadavers with active cancer, both solid and hematological. Such acceptance is based on the fact that the cornea is an avascular tissue and metastatic dissemination is extremely unlikely.

Methods. From a total of 588 corneal donors in the Sant Pau Tissue Bank (April 1999 to December 2003), 204 (34.7%) had an active malignancy or a history of malignancy. Of these, 177 had solid cancers and 27 had hematological cancers. Cancer was active in 94.7% and 64% had metastatic dissemination. A histopathological study of the 408 eyes from these 204 donors was performed to rule out metastasis. A total of 325 corneas (79.7%) were transplanted and recipients were followed for an average of 64.1 months (SD 11.1, range 30–86).

Results. The incidence of ocular metastases in the 204 donors with malignancy was 1%, 0.6% for solid cancer, and 3.7% for malignant hematological disease. There was no tumor transmission in any of the 325 recipients.

Conclusions. The incidence of ocular metastases in corneal donors with active malignancy is very low. Donor–recipient tumor transmission through corneal transplantation is highly improbable when the eyes are free of cancer.

Keywords: Cancer donor, Cancer transmission, Cornea donor selection, Corneal transplantation, Ocular metastasis.

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Between 30% and 40% of the total number of corneas available for transplantation may come from cancer donors (1–3). Acceptance of corneas from donors with solid cancers continues to be controversial, and this is even more so in the case of donors with malignant hematological disease. Such donors are not accepted by many European Eye Banks. However, only two cases of tumor transmission through corneal transplantation have been described in the literature (4, 5), with a third case reported at the 2003 Congress of the European Eye Bank Association (6). The first of the three cases was a primary retinoblastoma described by Hata in 1939 and the information provided was not sufficient to adequately document and confirm the case. The second report was the case of a donor with probable ocular metastases from a disseminated adenocarcinoma and the third case described the probable transmission of a small cell carcinoma of the lung.

Between 1999 and 2003, we histopathologically analyzed all the eyes from donors with cancer in our eye bank and we carried out an average follow-up of more than 5 years in the recipients. To the best of our knowledge, a clinical research protocol of these characteristics has not been published previously.

Materials and Methods

A total of 1,176 eyes from 588 donors were received in the Tissue Bank at the Hospital de la Santa Creu i Sant Pau from April 1999 to December 2003. Of these, 408 were from 204 donors who died from solid cancer or malignant hematological disease or had a history of past cancer (Table 1).

Donor Selection

All the corneal donors were patients who died at the center. Corneal donor selection criteria were those established by the Catalan Health Department Corneal Transplantation Advisory Committee (7). Those dying from an unknown cause, those with a background of viral infections or at high risk from the human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus, and those who presented degenerative diseases of the central nervous system were excluded as donors (7). Serological determination of anti-HIV1/HIV2 antibodies, Australia antigen, and anti–hepatitis C antibodies was performed on all donors (7, 8).

In the ocular evaluation, we excluded donors with structural anomalies, those with active ocular infection, and those with active or past history of herpetic keratitis. In relation to cancer, donors with primary ocular tumors were excluded (7). All those dying from systemic cancer, either solid or hematological, were accepted as corneal donors with the exception of patients who presented macroscopic evidence of ocular infiltration.

Enucleation, Validation, Preservation, and Transplantation of the Corneas

After enucleation, the cornea and the anterior chamber were studied with a slit lamp to rule out structural alterations. A corneoscleral button of 14 mm was then trephined and preserved in Optisol. An endothelial study was subsequently performed by noncontact specular microscopy, excluding corneas with guttae and those with endothelial counts less than 2,000 cells/mm² (8). Once validated, they were stored at 4°C, and transplantation was performed within the week of retrieved.

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From the total group of cancer donors, 86.8% had solid cancer and 13.2% had hematological cancer (Table 1). At death, active cancer was present in 94.7% of these donors, and 64% were diagnosed as having metastatic dissemination of their primary tumor.

### Histopathological Evaluation of the Eyes

No gross mass was detected in any eye and we did not find any cellular infiltration of the structures which make up the anterior segment in any of the 408 eyes studied by slit lamp. Metastases were not detected in any of the macroscopic cuts. Micrometastases were found in the histological sections stained with hematoxylin-eosin in two eyes corresponding to two donors, representing 1% of the 204 cancer donors and 0.5% of the 408 eyes analyzed (Table 2).

One of the eyes in which micrometastases was detected came from a donor with breast adenocarcinoma, a single focal infiltration of malignant cells being found in the posterior pole, in the choroid (Fig. 1A and B). The positive immunohistochemical staining for keratin Cam 5.2 confirmed the epithelial origin of the tumor mass (Fig. 1C). This represented metastatic involvement of 0.6% of the total number of donors with solid cancer and 0.3% of the eyes from this series (Table 2).

The other eye with microscopic metastases presented infiltration from chronic myeloid leukemia (Fig. 2A) and was confirmed by means of immunohistochemical staining with myeloperoxidase (Fig. 2B). The leukemic infiltrates were localized in both the anterior and posterior poles, mainly in sclera and episclera, with occasional foci in choroid and iris. This leukemic infiltration represented a metastatic involvement in 3.7% of the total number of donors with malignant hematological disease and in 1.8% of the total number of eyes from this donor group (Table 2).

### Follow-up of Corneal Recipients

We carried out a follow-up of the 325 recipients of corneas from donors with cancer for an average of 64.1 months (SD 11.1, range 30–86). A total of 305 (93.9%) of corneas were from donors with solid tumors, 64% of them had died with systemic dissemination of the neoplasia, and 20 (6.1%) from donors with malignant hematological disease (Table 1).

One of the 325 transplant recipients died as a result of an acute myocardial infarction 4 years after corneal transplantation, graft function was normal at the time of death. No cancer was transmitted in any of the 325 corneal recipients. Corneas from the two eyes that presented malignant cells in the microscopic study were also transplanted and there was no donor-recipient tumor transmission during the follow-up of 6.5 and 6 years, respectively.

During follow-up, de novo extraocular cancer was observed in two patients. Lateral basal cell carcinoma appeared in one recipient 3 years after transplantation with the cornea from a donor with disseminated breast cancer. The corresponding eye was negative for malignant cells. The second recipient, an 81-year-old male, was diagnosed with prostate carcinoma 4 years after transplant. He did not present occult neoplastic involvement. His corresponding donor had presented prostate carcinoma without local or systemic metastatic dissemination, and the study of the eyes was negative for malignant cells. The biomicroscopic appearance of the corneal grafts and the function of the corneal grafts of these

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**TABLE 1.** Tumor strain of corneal donors with cancer and of the corneas transplanted at the tissue bank of the Hospital de la Santa Creu i Sant Pau, 1999–2003

<table>
<thead>
<tr>
<th>Tumor Strain</th>
<th>Donors (%)</th>
<th>Corneas (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid cancer</td>
<td>177 (86.8)</td>
<td>305 (93.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>38 (18.8)</td>
<td>65 (20.0)</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>26 (13.2)</td>
<td>45 (13.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>23 (11.7)</td>
<td>39 (12.0)</td>
</tr>
<tr>
<td>Esophagus/stomach</td>
<td>15 (6.6)</td>
<td>32 (9.8)</td>
</tr>
<tr>
<td>Prostate</td>
<td>10 (5.1)</td>
<td>20 (6.1)</td>
</tr>
<tr>
<td>Ovary/uterus</td>
<td>10 (5.1)</td>
<td>20 (6.1)</td>
</tr>
<tr>
<td>Kidney/bladder</td>
<td>10 (5.1)</td>
<td>19 (5.9)</td>
</tr>
<tr>
<td>Pancreas/liver</td>
<td>11 (5.6)</td>
<td>19 (5.9)</td>
</tr>
<tr>
<td>Larynx</td>
<td>8 (3.6)</td>
<td>16 (4.9)</td>
</tr>
<tr>
<td>Brain</td>
<td>8 (3.6)</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td>Others</td>
<td>8 (3.6)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>10 (5.1)</td>
<td>16 (4.9)</td>
</tr>
<tr>
<td>Malignant hematological disease</td>
<td>27 (13.2)</td>
<td>20 (6.1)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12 (6.1)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>2 (1.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>5 (2.4)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>5 (2.4)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>8 (3.9)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>3 (1.5)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Non-Hodgkin</td>
<td>5 (2.4)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>4 (2.0)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Myeloproliferative syndrome</td>
<td>3 (1.5)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Refractory anemia and blasts</td>
<td>3 (1.5)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Total</td>
<td>204 (408 eyes)</td>
<td>325</td>
</tr>
</tbody>
</table>

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**RESULTS**

### Corneal Transplantation From Cancer Donors, Follow-up

A total of 325 of 408 corneas from cancer donors were transplanted in 325 recipients, and a clinical follow-up was performed for an average of 64.1 months (SD 11.1, range 30–86; Table 1). A complete ocular examination and systemic anamnesis were performed in the successive postoperative ophthalmologic visits: at 1 week, 1 month, and then bimonthly in the first year, and every 6 months during the second year.

### Corneal Donors in the Period 1999–2003

Cancer donors made up 204 of the 588 corneal donors at our center from 1999–2003, or 34.7% of the total number of donors.

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**Histopathological Evaluation of the Eye**

After removing the corneoscleral button, the rest of the eye underwent histopathological exam to rule out ocular metastatic involvement. Once fixed with formol, enucleated eyes were dissected on their meridional plane with horizontal cuts and evaluated by optical microscopy. The histological sections were stained with hematoxylin-eosin in two eyes corresponding to two donors, representing 1% of the 204 cancer donors and 0.5% of the 408 eyes analyzed (Table 2).

One of the eyes in which micrometastases was detected came from a donor with breast adenocarcinoma, a single focal infiltration of malignant cells being found in the posterior pole, in the choroid (Fig. 1A and B). The positive immunohistochemical staining for keratin Cam 5.2 confirmed the epithelial origin of the tumor mass (Fig. 1C). This represented metastatic involvement of 0.6% of the total number of donors with solid cancer and 0.3% of the eyes from this series (Table 2).

The other eye with microscopic metastases presented infiltration from chronic myeloid leukemia (Fig. 2A) and was confirmed by means of immunohistochemical staining with myeloperoxidase (Fig. 2B). The leukemic infiltrates were localized in both the anterior and posterior poles, mainly in sclera and episclera, with occasional foci in choroid and iris. This leukemic infiltration represented a metastatic involvement in 3.7% of the total number of donors with malignant hematological disease and in 1.8% of the total number of eyes from this donor group (Table 2).
two recipients were normal 4 and 5 years, respectively, after their transplants.

**DISCUSSION**

The percentage of corneas from cancer donors in our center (34.7%) was similar to the 30–40% of other series published (1–3).

To analyze the risk of cancer transmission from donor to recipient it is important to know the incidence of ocular metastases in the donors. In our study, this incidence was 1%, 0.6% for solid cancer, and 3.7% for malignant hematological disease. These results are lower than findings in previously published series of subjects dying with cancer in which the incidence reported is up to 12% for solid neoplasias and up to 66% for leukemia; most metastases were microscopic (Table 2) (9–12). This downward trend for ocular metastatic involvement may be due to earlier diagnosis of cancer and greater effectiveness of treatment in the last decades.

Localization of ocular metastases is mainly uveal (63%) and includes the choroid (88%), the iris (9%), and the ciliary body (2%), all richly vascularized tissues. It is followed in frequency by orbital (26%) and palpebral (10%) localization (13, 14). Leukemic infiltrates have been described in the optic nerve, in the retina and in the sclera, episclera, and conjunctiva (15–17), and exceptionally at the cornea where leukemic precipitates in the corneal endothelium (3) and corneal leukemic infiltrates (18, 19) have been observed. In our study, the micrometastatic localization was choroidal in the donor with breast cancer (Fig. 1) and in the donor with leukemia in sclera, choroid, and iris (Fig. 2).

Few studies in the literature have carried out a long-term follow-up of patients transplanted with corneas from donors with active, solid and hematological or primary ocular cancer. Wagoner et al. (2) performed a follow-up for an average of 10.5 years of 73 patients transplanted with 86 corneal grafts from cancer donors and they did not find transmission of the neoplasia. Salame et al. (3) carried out an average follow-up of 4 years in 40 recipients of corneas from cancer donors without finding transmission of malignancy. Harrison et al. (20) transplanted 47 corneas from patients with choroidal melanoma, confined to the posterior pole, and carried out a follow-up of 5.4 years without observing any cancer transmission.

In our series, none of the 325 patients transplanted developed ocular neoplasia. A labial epithelioma and a prostatic carcinoma were observed at 3 and 4 years, respectively, in two patients after transplantation. Although in the second case donor and recipient had a prostate carcinoma, we believe that it is highly unlikely that the tumor origin in the recipient was related to the neoplasia of the donor. This is firstly because the donor eye was analyzed microscopically and micrometastatic infiltration was not observed and secondly because the recipient has not presented an ocular tumor. Thirdly, prostate cancer has a prevalence of up to 70% in men more than 80 years of age (21, 22) and our recipient was 81 years old at transplant. Our follow-up group included the two recipients of the corneas from the two eyes that were positive for malignant cells; neither of them developed ocular or extraocular neoplasia.

Three cases of tumor transmission through corneal transplantation are reported in the literature. The first was

### Table 2. Histopathological study of the eye of subjects who died from solid cancer or malignant hematological disease

<table>
<thead>
<tr>
<th>Global</th>
<th>Malignant hematological disease and leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular microscopic metastases</td>
<td>Ocular microscopic metastases</td>
</tr>
<tr>
<td>Subjects/eyes (donors with leukemia)</td>
<td>[Donors with leukemia]</td>
</tr>
<tr>
<td>Subjects/eyes</td>
<td>—</td>
</tr>
<tr>
<td>Allen &amp; Straatsma, 1959–1960 (9)</td>
<td>—</td>
</tr>
<tr>
<td>Bloch &amp; Gartner, 1960s (10)</td>
<td>76 (50)</td>
</tr>
<tr>
<td>Elahi &amp; Bad et al., 1976–1980 (11)</td>
<td>93 (12.6%)</td>
</tr>
<tr>
<td>Nelson et al., 1973–1983 (12)</td>
<td>52 (7.3%)</td>
</tr>
<tr>
<td>Sant Pau Eye Bank, 1999–2003</td>
<td>177/354</td>
</tr>
<tr>
<td>—</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>204/408</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>204/408</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

*The cancer was the cause of death in all the subjects.*

*Includes carcinomas as cause of death (n = 562) or incidental carcinomas (n = 154). At least one eye was examined in each subject.*
described by Hata (4) in 1939 and consisted of the appearance of a retinoblastoma in the recipient of a cornea from a 54-year-old living donor in whom an eye was enucleated due to an infiltrating tumor of the anterior part of the optic nerve, papillary and peripapillary zone, and involvement of the posterior sclera with retrobulbar extension. The cornea, limbus, and the anterior eye chamber were not involved. The tumor was originally diagnosed by Hata as a glioma, but it was later classified as a retinoblastoma (1, 2, 5). Hata did not mention whether there was dissemination of the primary tumor or report on donor survival. Twelve months after transplantation, the recipient presented a tumor in the periphery of the cornea and limbus extending to the anterior and posterior chamber through the ciliary body. Enucleation was performed and histopathological analysis confirmed the origin. Two years after enucleation, there was no systemic cancer dissemination and the recipient was in a good health.

The second case of transmission was published by McGeorge et al. (5; personal communication) in 2002. Confirmation was performed by molecular analysis. It consisted of a mass in the iris of a corneal recipient 19 months after transplantation. This ocular mass coincided histologically and genetically with the sample taken by percutaneous biopsy from a pulmonary lesion in the donor 6 months before death. The primary tumor of the donor was thought to originate from the bowel. After excisional biopsy and local radiotherapy of the mass in the iris, no ocular relapses or systemic metastases were observed in the 10-year follow-up and the corneal graft remained transparent. Choroidal masses, compatible with metastases, had been observed in both donor eyes. These masses were not histologically examined. The cornea and the anterior chamber were examined by slit lamp shortly after retrieval and no abnormal features were noted. The cornea was stored at 4°C for 2 days before being transplanted. Neither ocular nor systemic cancer appeared in the recipient of the cornea from the contralateral eye from the same donor.

The third case was presented at the European Eye Bank Association (EEBA) Congress of Brussels 2003 by Florén et al. (6; personal communication). A 76-year-old male received his second corneal graft on the same eye. Four months later the regrafted eye presented an inflammatory reaction and cytology of the vitreous humor revealed malignant cells. No primary cancer was found and 11 months after transplantation the eye was enucleated. Histopathology revealed multifocal small cell carcinoma invading the posterior surface of the cornea, the anterior chamber angle, anterior surface of the iris, retina, and choroids. The 75-year-old male cornea donor had died from a widely disseminated small-cell carcinoma of lung. These eyes did not present any ocular mass or any gross lesions of any kind at retrieval. They were not studied by slit lamp and did not undergo histopathological exam. The corneas were not stored and were kept for a short term at room temperature before being transplanted to two recipients. Donor and recipient tumors presented great histopathological resemblance. Human leukocyte antigen (HLA)-DR alleles found in the recipient tumor were HLA-DR1, -DQ5 and in recipient somatic cells were HLA-DR1, -DR17(3), and -DR4. Unfortunately, the donor tissue was not appropriate for HLA analysis. Ten years after the corneal transplantation, the recipient was in good health without malignancy. The follow-up of the recipient who received the counterpart cornea from the same donor was uneventful.
Based on these three cases, donor selection criteria universally contraindicate the use of corneas from donors with retinoblastoma, primary or metastatic ocular adenocarcinoma, and any tumor affecting the anterior segment of the eye (7, 23, 24). Some European and American eye bank protocols do not contraindicate the use of corneas from donors with choroidal melanoma, provided that they are confined to the posterior segment of the eye, given that tumor transmission has not been demonstrated to date with corneal transplantation from these donors (20). Many other protocols do not contraindicate corneas from donors with systemic solid neoplasia as long as there is no ocular involvement (7, 23, 24).

No cases of transmission of hematological cancer through corneal transplantation have been reported to date. However, ocular micrometastases of hematological cancer, above all leukemia, is between 6 and 15 times more frequent than of solid cancer (Table 2). The greater and constant presence of malignant cells in the blood stream in hematological cancers may account for the greater accessibility of these cells to all the tissues. Although leukemia can infiltrate any tissue, it does not generally affect the cornea (25). Most tissue banks worldwide contraindicate the use of hematological cancer donors. European Eye Bank Association (EEBA) standards (23) exclude cadavers with leukemia, lymphoma or myeloma as cornea donors and the EEBA standards (24) contraindicate those with leukemia or active disseminated lymphoma.

Tumor transmission through corneal transplantation is highly unlikely for several reasons. The first is that metastatic dissemination is improbable in a nonvascularized tissue such as the cornea. The second is the fact that the mass of neoplastic cells that could be transferred with this transplantation is very small. Finally, as treatment with systemic immunosuppression in corneal recipients is exceptional, the recipient remains immunocompetent and cancer proliferation is prevented. One of the possible pathogenic mechanisms that could be involved in the transference of malignant cells to the cornea has been proposed by Deb-Joardar et al. (26). Their hypothesis is that the transmission of malignant cells from donor to recipient could take place during the process of corneoscleral excision and storage. These authors demonstrated that when the cornea is stored at culture at 31°C, malignant cells could survive and proliferate in the culture medium. These cells would later adhere to the inner face of the cornea in those areas deprived of endothelial cells during its storage.

Despite the exceptional possibility of donor-recipient cancer transmission through corneal transplantation, we suggest three sequential steps that should be followed in the selection of corneas for transplantation from donors with cancer: 1) eyes that present macroscopic tumor masses should be rejected; 2) the cornea and anterior chamber of the eye should be carefully evaluated by slit lamp to discard tumor infiltration; and 3) histopathological study of the eye should be performed prior to corneal transplantation and cornea should be rejected in cases of tumor cellular infiltration.

In addition, during the first 2 years after transplantation, we recommend a careful follow-up of the recipient. It should be kept in mind that benign disorders such as sarcoid nodules or secondary amyloidosis may appear in the corneal graft and mimic tumors (27, 28).

In conclusion, results from this study suggest that ocular metastatic involvement in patients dying from active solid or hematological cancer is currently very low and transmission of malignancy is highly unlikely when there is no tumor infiltration of the eye. Corneal donors with active cancer represent a high percentage of corneas viable for transplantation.

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