MANAGEMENT OF RECIPIENTS OF HEPATIC ALLOGRAFTS HARVESTED FROM DONORS WITH MALIGNANCY DIAGNOSED SHORTLY AFTER TRANSPLANTATION

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Running title: Cancer in liver graft

Computer System: Macintosh OS 8, Microsoft Word 6.0

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Detry O, Honoré P, Jacquet N, Meurisse M. Management of recipients of hepatic allografts harvested from donors with malignancy diagnosed shortly after transplantation.

Clin Transplantation

Abstract: Transmission of undiagnosed malignancy with the graft is a dramatic complication of liver transplantation. Alternatives in the management of the recipients of livers harvested from donors with malignancy diagnosed shortly after transplantation, are either early retransplantation or close follow-up without reoperation.. We reported four cases of liver recipients whose allografts were harvested from donors who were diagnosed with malignancy shortly after the liver transplantation. One recipient underwent retransplantation, and the three other allografts were not removed. No recipient developed recurrence in the follow-up. While graft removal may be the only way to avoid tumor recurrence in recipients of liver graft harvested from donor with malignancy, close follow-up without reoperation may also be considered. The risk of tumor transferral may depend on the histopathological aggressiveness an metastatic potential of the donor tumor, and may be low for low-grade, local tumors. This risk should be evaluated by analysing large series, using databases of Eurotransplant or United Network for Organ Sharing.

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Malignancy transmission from the donor to the recipient is a rare but dramatic complication of solid organ transplantation. In our institution, one kidney and one liver recipient both developed recurrence of an undiagnosed choriocarcinoma that led to donor's death (1). Since these two cases, we have received from Eurotransplant two liver allografts which were harvested from donors with undiagnosed malignancy, and that were transplanted in our institution. We also diagnosed a renal-cell carcinoma in a renal graft, whose corresponding liver was split and transplanted into two recipients in two other centers.

Management of the recipients of liver allografts harvested from donors with malignancy diagnosed shortly after transplantation, has not been established because only a few cases have been reported in the literature. The alternatives are either early retransplantation or close follow-up without reoperation in order to detect any recurrence. Based on our first unfortunate experiences and on the literature (2), we initially recommended early retransplantation (1). We successfully applied this policy in a recipient of a liver whose donor was later diagnosed with a disseminated epidermoid epithelioma. However, we recently chose not to retransplant the recipient of a liver graft harvested from a donor with undiagnosed renal-cell carcinoma. The purpose of this paper was to report these cases and to explain the changes in our management policy.

Case Series

Recipient 1

In June 90, Eurotransplant sent us an hepatic allograft harvested from a 35-year-old female donor, who had died from spontaneous cerebral hemorrhage. We transplanted this graft into a 25-year-old recipient. Donor autopsy was performed the day after the harvest. This autopsy and the histopathological examination of several lymph nodes demonstrated a disseminated, invasive, epidermoid epithelioma originating from the cervix uteri (1). The recipient was then screened for gross tumor involvement of the liver graft using ultrasonography and computed tomography. No evidence of tumor was showed. The patient was listed for emergent retransplantation and underwent a second orthotopic liver transplantation (OLT) seven days after the first transplantation. No evidence of any malignant process was detected during the reoperation and on histopathological examination of the explanted liver. The patient remained free of recurrence at the 7-year follow-up.

Recipients 2 and 3.

In August 96, we received from Eurotransplant a kidney graft harvested from an 18-year-old donor who had died from head trauma. The multiorgan procurement had been uneventful. We discovered a 2 mm renal-cell carcinoma in this kidney, and the transplantation was cancelled. However, at the time of histopathological diagnosis, the liver from this donor had already been split and transplanted into two recipients in two different institutions. Despite this diagnosis, the liver grafts were not removed. These two recipients

remained free of recurrence at the 1-year follow-up, as established by telephone contact with the institutions where the organs were transplanted.

Recipient 4.

In October 97, we received a liver allograft harvested from a 54-year-old male donor who had died from spontaneous subdural hemorrhage. We transplanted this liver into a 49-year-old male recipient. Shortly after graft reperfusion, the procurement team announced the discovery of an 8 mm renal-cell carcinoma in the right kidney. We carefully examined the liver graft, and performed an intraoperative ultrasonography. No evidence of metastasis was found and the OLT was completed. After discussion, we decided not to remove this graft. This recipient died from graft versus host disease 7 months after OLT. No evidence of tumor recurrence was found at autopsy and on histopathological examination of the liver.

Discussion

The first reports of malignancy transferral with solid organ transplantation were published in the 1960's, when the risks of cancer transmission into immunosuppressed patients were not known (2). Today, it has become obvious that the immunosuppressive treatment enhances the risk of tumor recurrence in recipients of organs harvested from donors with malignancy (3). Therefore, with the relative exception of the primary central nervous system tumors (2,4,5), patients with recent known history of malignancy are actually rejected for organ donation. Moreover, donors should be carefully screened for undiagnosed or infraclinic malignancy (1,6). Based on our unfortunate experience of tumor transferral in two recipients, we recommended a severe policy of tumor detection in the donor (1), based on (a) the careful examination of the donor during procurement; (b) the immediate frozen section of any suspicious lesion; (c) intraoperative ultrasonography of liver and kidney grafts; (d) donor autopsy; (e) beta-human chorionic gonadotrophin (ßHCG) screening in all female donors in child bearing age, in order to diagnose choriocarcinoma. Using this policy, we recently discovered a undiagnosed renal-cell carcinoma in a donor who had died from spontaneous cerebral hemorrhage, and we cancelled the procurement (6). However, this policy can not completely avoid transplantation of grafts harvested from donors with undiagnosed malignancy because (a) some tumors can be too small to be diagnosed by examination or intraoperative ultrasonography (7); (b) immediate frozen sections are not available in every procurement hospital, and/or their results may be communicate to late (1,7); (c) intraoperative ultrasonography is not available in many community hospitals (7); (d) permission for donor autopsy is seldom given (7); (e) ßHCG testing is not available in every hospital (7); (f) the

organ donor shortage has lead to the use of "suboptimal" and/or older donors, whose risk of undiagnosed malignancy is increased (6); (g) the thoracic organs are usually harvested and transplanted prior to any extensive donor dissection (8). Consequently, there will always be sporadic cases of transplantation of grafts harvested from donors with undiagnosed malignancy.

Management of the recipients of liver grafts harvested from donors with malignancy diagnosed shortly after the OLT, can be a matter of debate. The alternatives are either early removal of the liver graft and recipient retransplantation (2), or close follow-up without reoperation. Based on our experience, we initially recommended early retransplantation (1). We successfully applied this policy in Recipient 1, who was still alive without recurrence at the 7-year follow-up. However, we did not find evidence of malignancy in the explanted graft, and it is likely that this recipient could have remained tumor free without reoperation. In Recipients 2 and 3, the surgeons who transplanted the two parts of the corresponding liver did not retransplant the recipients despite our diagnosis of renal-cell carcinoma in a kidney graft. Recently, we chose not to retransplant Recipient 4, despite the evidence of an 8 mm renal-cell carcinoma in the donor. This policy change may seem controversial, because early retransplantation could be the only way to avoid malignancy recurrence in the recipients. However, retransplantation should be recommended only if the benefits in the decrease in the risk of tumor recurrence are greater than the risks and the costs of the retransplantation.

It is difficult to estimate the risk of malignancy transmission after transplantation of a liver graft harvested from a donor with malignancy. This risk depends certainly on several factors, as the type, the size and the grading of the tumor, as well as the type of post-

transplantation immunosuppressive regimen. It is well known that the liver is a usual metastasis site and the risk of recurrence after liver transplantation is therefore irrefutable. For instance, it is estimated that more that 25 percent of patients with renal-cell carcinoma have metastases at the time of diagnosis, and that the liver is a site of metastasis in 30 to 40 percent of the cases (9). Since the 1960's, the Cincinnati Transplant Tumor Registry (CTTR) has collected reports of tumor occurring in transplanted patients. The CTTR has also recorded the discoveries of malignancy in organ donors, including primary brain tumors. According to this registry, 248 recipients received organs from such donors up until 1995, and 103 of these recipients (42%) developed tumor recurrence (7). However, we believe that the overall risk of recurrence after OLT is still unknown. Most of the CTTR cases involve kidney grafts. As a matter of fact, up until 1995, only 10 liver recipients whose organ donors were diagnosed with malignancy, were listed in the CTTR (7). Furthermore, the high recurrence rate reported by the CTTR may be biased, as it is easier to report a complication, such as tumor transferral, than to report the absence of complication, such as the absence of tumor transferral. In the absence of study on the outcome of recipients of liver harvested from donors with undiagnosed malignancy, we consider that the risk of tumor transferral with liver graft is still unknown. This risk may be lower than previously published and may depend on the histopathologic aggressiveness and metastatic potential of the donor tumor. This risk may be moderate for local, low-grade tumors, or if the intraoperative ultrasonography of the liver graft shows no evidence of metastasis.

The immediate removal of the liver graft after diagnosis of donor's tumor can not avoid the risk of tumor recurrence from malignant cell seeding and dissemination at the time of graft reperfusion. The risks and the costs of early retransplantation must also be considered. The

morbidity and the mortality of reoperation is not negligible. Retransplantation also consumes an additional liver allograft, during a time when many patients awaiting for OLT are dying because of the organ shortage. For all these reasons, early retransplantation may appear to be a costly and high risk procedure, whose effectiveness for avoidance of tumor recurrence has yet to be established.

In conclusion, removal of a liver graft harvested from a donor with malignancy diagnosed shortly after OLT, may be the only way to avoid tumor recurrence in the recipient. However, in the absence of study demonstrating the efficacy of early retransplantation, close follow-up without reoperation is certainly an alternative, especially for low-grade, local tumors. The risk of tumor transferral should be studied by analysing the outcome of large series, using the databases of Eurotransplant or the United Network for Organ Sharing. Such a study could lead to a rational scientific approach to the management of recipients of hepatic allografts harvested from donors with undiagnosed malignancy.

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