Donor-Transmitted Cancers in Transplanted Livers: Analysis of Clinical Outcomes

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Donor-Transmitted Cancers in Transplanted Livers: Analysis of Clinical Outcomes

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Abbreviations: CI, confidence interval; DDC, donor-derived cancer; DRC, donor-related cancer; DTC, donor-transmitted cancer; GBM, glioblastoma; HR, hazard ratio; IQR, interquartile range; OS, overall survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD, standard deviation.

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Abstract

The risk of transmission of malignancy from donor to recipient is low; however, this occurrence has dramatic consequences. Many reports of donor derived cancers in liver transplant recipients have been published, but they have not been a systematically summarized into a lucid and unified analysis. The present study is an attempt to provide clarity to this unusual, but clinically important problem. We systematically reviewed all case reports, case series, and registries published on cancer transmission events through the end of December 2019. We identified a total of 67 publications with 92 transmission events. The most frequently transmitted cancers were lymphomas (30 [32.6%]), melanomas (8 [8.7%]), and neuroendocrine tumors (8 [8.7%]). Most of the melanomas were metastasizing, while most of the lymphomas were localized to the graft. The median time to cancer diagnosis after transplantation was 7 months, with 78% of diagnoses established in the first year. Melanoma carried the worst prognosis, with no recipients alive at 1 year after cancer diagnosis. Lymphoma recipients had a better outcome, with more than 75% surviving at 2 years. *Conclusion:* A metastatic cancer carries a worse prognosis for recipients, also because recipients with localized cancer can benefit from the chance to undergo transplantation again. The findings confirm the need to pay attention to donors with a history of melanoma but also suggest the need for a more careful evaluation of groups of donors, such as those dying from cerebral hemorrhage. Finally, recipients of organs from donors with cancer should be carefully followed to detect potential transmission.

Transplantation is the best therapeutic option for patients with end-stage liver disease, with the benefits for survival and quality of life greatly exceeding the risks. An important risk is the development of de novo cancer due to immunosuppression. In addition, transplantation of an organ from a donor to a recipient

carries a risk transmission of diseases, such as cancer. Cancer transmission from a donor was originally recognized in kidney transplant recipients, and many case reports have been published.[1] Donor-related cancer (DRC) can be divided into donor-transmitted cancer (DTC) in which the malignancy is present or presumed present in the graft at the time of transplantation or donor-derived cancer (DDC) in which cancer is not present but develops within donor cells after transplantation.[2,3] Although this definition is theoretically useful, a clear distinction is not always possible in practice.[2] Ison et al.[3,4] set out a framework for a definition of proven, probable, or possible transmission event, but they also state that it is currently not possible to assign these categories on the basis of a single time point.[3] The incidence of DTC appears to be low according to large series of donors with a history of malignancy or ongoing malignancy[5-8]; however, there is still concern regarding the safe use of such donors and how to prevent transmission events. Moreover, international guidelines and recommendations[9-12] on the level of risk are mainly based on case reports or small case series published across a long time span and in different transplant settings.[13] Most available literature concerns renal transplant recipients. Compared to livers, kidneys are far less often involved with metastases,[14] and therefore the incidence in liver recipients may be higher.

The aim of this study is to systematically review all the published evidence on cases of DRC in liver transplant recipients to provide insight on cancer-specific survival and assess recipient and transplant factors that influence recipient outcome.

Methods

We conducted a systematic review according to standard methods and reporting in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15] No institutional review board approval was needed because no ethical issue is raised by literature reviews.

Search strategy and databases

A systematic search was carried out without any language restrictions in the electronic databases PubMed, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) through December 31, 2019, to identify any study documenting transmission of cancer from donor to liver transplant recipient. An additional search was performed in ClinicalTrials.gov and Grey literature resources (opengrey.eu, oaister.worldcat.org). Full texts assessed for eligibility also underwent reference hand-searching to identify relevant articles that could potentially be missed.

The key terms “transplantation,” “transmission,” “donor,” “cancer,” “tumor, and “malignancy” were adequately combined in their variations for all the databases (Supporting Appendix S1).

Inclusion and exclusion criteria

Two investigators (Ilaria Girolami, Stefano Marletta) independently screened titles and abstracts with the aid of the Rayyan Qatar Computing Research Institute (QCRI) reference manager web application.[16] Disagreement was resolved by consultation with the senior researcher (Albino Eccher). Any article documenting a DTC or DDC in a liver recipient according to the Disease Transmission Advisory Committee (DTAC)[4] was included. Exclusion criteria were: i) non-liver recipients; ii) the only transmission of oncogenic viruses considered to be a predisposing factor to tumor development but with no documented cancer of donor-origin. Lack of description of a recipient's outcome was not considered sufficient to exclude an article if other relevant information was present. Any type of study that contains data pertinent to a transmission event was included, even in the case that the article was not mainly dealing with a liver transplant but it reported a brief note on the liver recipient (e.g. report of a transmission event in a kidney recipient from a multiorgan donor which reports also a note on the liver recipient). Editorials, letters, and review articles were excluded, but their reference lists were hand-searched. When more than one publication was present for the same case of a transmission event, the more detailed article was included. Full texts of articles fulfilling the initial screening criteria were reviewed for subsequent inclusion.

Data extraction

Two authors independently extracted data from the included studies following a standardized extraction form. Data extracted were donor age and sex, recipient age and sex, cancer type and site if localized to the graft or metastasizing, treatment of the recipient, prior cancer history in the donor, whether the donor was a multiorgan donor, whether and how the donor was evaluated, donor cause of death, methods of establishing donor origin of cancer, time to cancer diagnosis in recipient after transplantation, outcome of recipient, time to death from cancer diagnosis, and whether death was due to cancer.

The primary outcomes were the time to cancer diagnosis and the overall survival (OS) of recipients after cancer diagnosis. The secondary outcomes were the distribution of cancer types, frequency of metastasizing malignancies, and impact of retransplantation as a treatment for localized malignancies.

Quality assessment

Quality of studies was assessed according to a standardized checklist for quality assessment of case reports and case series.[17] The items of the checklist were modified, tailored to the specificity of a cancer transmission event. The checklist comprised description of the following: donor's and recipient's demographics, donor's cause of death, donor's evaluation at procurement, method to establish donor origin of tumor, time from transplantation to cancer diagnosis, type and site of cancer, whether localized or

metastasizing, recipient's treatment, follow-up time, recipient's outcome, and whether death was due to transmitted cancer. Adequate follow-up time was defined a priori as at least 6 months or until the recipient's death, following previous reporting.[1]

Data synthesis and statistics

A descriptive synthesis of demographic data of donors and recipients, types and sites of malignancies, donors' evaluation, and recipients' treatment was provided. Continuous measures were expressed as mean with standard deviation (SD), median, and range, and dichotomous variables were expressed as numerical values and percentages.

Time-to-event curves were calculated using the Kaplan-Meier method for overall recipients and for the three most frequent transmitted malignancies. Cox proportional hazard analysis was used to assess the impact of clinical variables (age, gender, site of cancer, treatment other than retransplant) on recipients' survival. Univariable regression models were fitted for the overall population of recipients and in the sub-population of most frequent cancers, and for multivariable regression analysis a backward selection of variable was performed at $p = 0.20$ for inclusion. In the subgroup of most frequent cancer, histotype was considered an additional variable. The absence of multicollinearity was verified with variance inflation test. Statistical significance was set at 0.05. All analyses were carried out with the open-source statistical software R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Literature search

Of the 9,271 publications, following removal of duplicates, 8,956 were excluded after title and abstract screening. The remaining 315 were assessed in full-text form. Of these, 67 articles were included. The included studies comprised 45 case reports (n = 45 cases), 16 case series (n = 33 cases), and 6 registries (n = 14 cases), with a total of 92 recipients. Each case of a recipient with DRC corresponded to a single liver donor. The flow of article screening is depicted in Fig. 1.

Quality appraisal

The quality appraisal is shown in Supporting Fig. S1. The overall quality was adequate, with more than 70% of cases with clear information in 6 out of 11 items. Information on the recipients' outcome, adequate follow-up, and whether death was due to cancer was present in all cases and clear in more than 90% of cases. Time to cancer diagnosis was lacking in 6 cases (6.5%), and site of cancer was clearly reported in 73

(79.3%) of cases. Clear demographic data of recipients were more frequent than clear donor data (71 [77.2%] versus 54 [58.7%]). Clear information regarding the method to establish the donor origin was reported in 57 cases (62%). The less commonly reported items were evaluation of donor at procurement (49 [53.3%] with missing information), donor's cause of death (42 [45.7%] with missing information), and donor demographic data (32 [34.8%]).

Characteristics of donors

The main characteristics of donors are reported in Table 1. All donors were deceased, of which 49 (53.3%) were multi-organ donors, 3 (3.3%) donated the liver only, and the information was not stated in 40 (43.5%). The mean age of all donors was 45.6 years (SD, 20.4) (range, 1-81 years; median, 47.5) but varied by cancer types, with a mean age of 29.5 years (16.8) and 31 years (4.8) for donors transmitting lymphoma and choriocarcinoma, respectively, and a mean age of 69 years (7.5) and 50 years (5.7) for donors transmitting colorectal carcinoma and melanoma, respectively. Sex was not stated in 34 cases (37%), whereas male and female donors were 30 (32.6%) and 28 (30.4%), respectively. There was a known history of cancer or a malignancy present at procurement only in eight cases (8.7%), of which five (62.5%) were glioblastoma (GBM) patients. Causes of death were available in 50 cases (54.3%), of which 31 (62%) were cerebrovascular events (cerebral hemorrhage/hemorrhagic stroke). Nine cases (18%) reported head trauma/accident, and the remaining eight donors died from other causes, with three with GBM dying after surgery for the disease. A total of 43 cases provided information on evaluation at procurement, with 21 detailing information: 10 underwent some imaging study, 7 only clinical exam and blood tests, 1 a biopsy, and 3 cases a complete autopsy.

Characteristics of recipients

The main characteristics of recipients are shown in Table 2. The mean age of all recipients was 49 years (SD, 14.2) (range, 1-73 years; median, 52) but varied by cancer types, with a mean age of 23.7 years (SD, 8.4) for recipients with GBM and 59.6 years (SD, 4.8) for recipients with colorectal cancer. Of the recipients,53 (57.6%) were male; however, sex was not reported in 19 (20.7%). Cancer was localized to the graft in 46 cases (50%) and metastasizing in 29 cases (31.5%), whereas in 17 (18.5%) cases this information was not reported or was unclear. Cancer was limited to the graft in more than 80% of lymphomas and in all five colorectal cancers, whereas 100% of choriocarcinomas, 80% of GBMs, and 62.5% of melanomas were metastatic. Recipients were treated with tumor excision or retransplant in 25 cases (27.2%), with chemotherapy alone in 24 (26.1%) and reduced immunosuppression alone in 9 (9.8%), whereas in 5 cases (5.4%) there was only supportive or no treatment, and in 29 cases (31.5%) the information was missing or unclear.

Frequencies of malignancy

Of all 92 cases, 30 (32.6%) were lymphomas, followed by melanomas (8 [8.7%]) and neuroendocrine malignancies (8 [8.7%]). Choriocarcinomas, GBMs, and colorectal cancers represented 5 (5.4%) of cases. Other malignancies included 5 (5.4%) sarcomas, 3 (3.3%) high-grade undifferentiated malignancies, and 2 (2.2%) other central nervous system (CNS) tumors (full list in Supporting Appendix S2).

Outcome of overall recipients

The time to diagnosis for the overall population of recipients is shown in Fig. 2. The median time to cancer diagnosis was 7 months (interquartile [IQR], 5-12) and at 1 and 2 years, 78.1% and 90.3% of recipients, respectively, have been diagnosed. There was no significant difference between males and females (log-rank test, $P = 0.52$) or between localized or metastasizing malignancies (log-rank test, $P = 0.86$).

The overall survival (OS) for the overall population of recipients after cancer diagnosis is shown in Fig. 3. The median OS was 37 months (IQR, 2-78), with 55.7% and 51.8% of recipients alive at 1 and 2 years after cancer diagnosis, respectively. There was no significant difference according to sex (log-rank test, $P = 0.19$). The median OS for recipients with a metastasizing malignancy was 2 months (IQR, 1-9), whereas recipients with localized malignancies did better (log-rank test, $P < 0.0001$), so it was not possible to determine the median survival, with 87.7% recipients alive at 24 months and at end of available follow-up. In univariable regression analysis, the recipient age did not appear to be associated with OS (hazard ratio [HR], 1.86; confidence interval [CI], 0.89-3.88; $P = 0.10$), and the metastatic localization of cancer was the strongest prognostic factor associated with a bad outcome (HR, 13.58; CI, 4.61-40.04; $P < 0.0001$). Gender was not associated with OS (HR, 1.70; CI, 0.77-3.75; $P = 0.19$), as was treatment other than retransplant (HR, 2.14; CI, 0.86-5.59; $P = 0.10$). In the multivariable regression analysis, only metastasizing cancer retained a strong adverse prognostic value (HR, 12.56; CI, 3.85-40.97; $P < 0.0001$; gender HR 1.11 [0.45-2.74] $P = 0.82$; age HR 2.1 [0.84-5.32] $P = 0.11$; treatment HR 2.72 [0.95-7.73] $P = 0.06$). No multicollinearity was detected (highest VIF 1.12). The results of survival analysis are summarized in Table 3.

Subgroup of the most frequent tumors

The time to diagnosis for the most frequent cancer types is shown in Fig. 4. The median time to diagnosis was 7 months (IQR, 4-8) for lymphoma, 9 months (IQR, 6-15) for melanoma, and 9.5 months (IQR, 8-12) for neuroendocrine malignancies (log-rank test, $P = 0.003$). All melanomas and lymphomas were diagnosed in the first 2 years after transplantation, whereas a case of neuroendocrine tumor was discovered after 5 years.

The OS for the three most frequent tumors is shown in Fig. 5. Recipients with lymphoma had better survival than recipients with melanoma or neuroendocrine tumors (log-rank test pair-wise comparisons with post hoc correction, $P < 0.0001$ and $P = 0.02$, respectively), with approximately 79% of lymphoma recipients alive at 2 years after diagnosis. The median OS for melanoma and neuroendocrine cancer recipients was 1 month (IQR, 0.5-2) and 9 months (IQR, 6-48), respectively. Of the eight neuroendocrine cancer recipients, five (62.5%) died of the disease, but complete data on follow-up time were missing for one of them. Of the eight melanomas, complete follow-up data were missing for three of them, but the other five all had metastasizing malignancy and died from disease at 1 year after diagnosis. In univariable regression analysis, a diagnosis of melanoma or neuroendocrine cancer was associated with worse prognosis with variable statistical significance. As shown in Table 3, for melanoma the HR was 18.12 (4.38-75.07), $P <0.0001$. For neuroendocrine cancer, the HR was 4.79 (1.19-19.32) P = 0.03. However, in the multivariable model the HRs for these cancers were not statistically significant (melanoma HR 6.20 [0.16-248.01] $P = 0.33$; neuroendocrine HR 11.06 [0.17-711.42] $P = 0.25$). None of the other variables that entered the multivariable analysis reached significance to be kept in the model. No multicollinearity was detected (highest VIF 4.77). The results of survival analysis are summarized in Table 3.

Other outcomes

In the subgroup of recipients with localized cancer, tumor excision followed by retransplant or retransplant alone was the treatment of choice in 18 cases (39.1%). In this subgroup, for recipients undergoing retransplant, there was a tendency to better survival than recipients treated with chemotherapy or only reduction of immunosuppression; however, this did not reach statistical significance ($P = 0.11$, not shown). Chemotherapy alone was the most common treatment of lymphoma patients (11 out of 30 [36.7%]), and excision and retransplant/retransplant alone was the treatment in 80% of colorectal cancer recipients, all of which were limited to the graft. None of the melanoma recipients underwent retransplant, and three cases they (37.5%) were treated with chemotherapy alone.

Discussion

Because of this imbalance between the supply and demand for organs, to increase the donor pool, donors with a history of, or a current diagnosis of, malignancy are being considered by some centers. Although the risk of cancer transmission appears to be low, with reported incidences of approximately 0.03% to 0.06%, a transmission event has severe consequences.[5,18-21] This has been studied the most in renal recipients, and our aim was to provide some insights on the outcome and characteristics of the liver transplant recipients with transmitted cancer, given also that no clearly systematic study on the topic is present to date in

literature[2] and that livers in theory are more likely to "carry" tumor cells because they are more often the site of metastases.[14] Publications on cancer transmission in the liver are less numerous than in kidney recipients where this issue has been already systematically explored.

The present study suggests that, in most cases, the diagnosis of cancer is made soon after transplant, with 78% of recipients developing transmitted cancer before 12 months. Although transmission is a rare occurrence, a higher index of suspicion while managing patients in the first posttransplant year is warranted.

According to our findings, melanoma and neuroendocrine cancers have the worst prognosis, with no melanoma recipients alive at 2 years and 40% overall survival for neuroendocrine cancer. In comparison, the prognosis of recipients developing lymphoma is more favorable, with a 2-year survival rate of more than 75%. A similar review on kidney recipients by Xiao et al. in which lymphoma and melanoma were among the most common transmitted cancer, showed survival results comparable to ours.[1] The findings for melanoma are not surprising because the immunological background plays an important role in melanoma. Melanoma cells that have been dormant in the donor for years can reactivate in an immunocompromised host and give rise to a metastatic spread.[22] At the same time, new available treatments with immune checkpoint inhibitors can offer an important therapeutic chance, as already seen in kidney recipients with transmitted melanoma.[23] Although the findings on the neuroendocrine tumors are partly unexpected, as it has some similarities with melanoma, with early onset, widespread metastases, and a bad prognosis, it could warrant further investigation of possible immunological interactions.[24] Furthermore, poor prognosis of transmitted neuroendocrine tumors makes their discovery even more important and could suggest the opportunity for blood tests for hormone-producing tumors in the donor. Survival curves were not obtained in other cancer groups because of the extremely low numbers, but we can point out some observations. All five choriocarcinomas had metastasized at time of diagnosis, and all the recipients died of disease. Similar findings apply to GBM recipients, with 80% metastatic malignancies and three out of five dying of the disease. On the contrary, all colorectal cancers were limited to the graft, and only the recipient not undergoing retransplant died of the disease.[25] These findings suggest that caution is advised in using organs from donors with high metastatic potential malignancies, weighting also the risk factors in single cases, whereas for other malignancies, if localization is limited to the graft, retransplantation, together with the new immunotherapy treatments, could be a feasible option.[23]

Localization of tumor to the liver appears to be the most important factor influencing outcome. Metastatic disease at diagnosis is the strongest adverse prognostic factor, and this is reasonable because cancer metastatic spread requires the recipient to undergo chemotherapy and precludes the chances of early retransplantation. This is compounded by the inability to stop or significantly reduce immunosuppression in

liver recipients in order to achieve an immunological response against the donor cancer because, unlike in renal transplantation, there is no possibility of easy replacement therapy and returning to the waiting list.

Consideration also needs to be given to management of the donors to identify potential risks. The donor had a clear history of cancer in only 8.9% of cases, and five of these were the GBMs. These, however, were from decades ago when donors with CNS malignancy were used even in the presence of risk factors such as surgery and ventricular shunts. Such cases are less likely to occur today because of their recognized risks.[11,12] Evaluation of the donor is the item that is reported less frequently in an adequate manner, so we can only speculate on the consequences of a more careful evaluation. Autopsy led to the early discovery of cancer and prompted urgent retransplantation in one case.[26] Routinely performing autopsies is now not considered cost-effective due to the low pickup rate and because it is not always accepted by families; therefore, a balanced use of radiological examinations should be part of the donor evaluation. An extensive instrumental/invasive evaluation of the donor is not viable or cost-effective because donors in intensive care units are clinically unstable, with risk of organ damage. Recipients in life-threatening conditions cannot wait until results are available, so the opportunity to receive a transplant should be balanced against a transmission risk that has shown to be low. Cerebral hemorrhage is the most frequently reported cause of death in our study donor population, i.e. those with associated cancer transmissions; some of the tumors from these donors could be metastasis of unknown primary, so particular attention should be paid to donors with cerebrovascular hemorrhagic accidents of young age or without stroke risk factors. Indeed, a similar consideration is present in the early reports of choriocarcinoma transmission dating back to the late 1980s to early 1990s in which the donors were all young women dying of cerebral hemorrhage with no cerebrovascular risk factors.

Lymphoproliferative neoplasms are unlikely to be discovered before transplantation in the time constraints of donor evaluation because a neoplastic clone present in the donor cannot be discovered with routine evaluation, and therefore there will always be a risk of transmission. Thus, a high level of suspicion during the first 2 years after transplantation to allow early detection is warranted. As already stated elsewhere, there is still ongoing controversy regarding whether lymphoma should be defined as DDC or DTC,[1,27] with the majority of posttransplant lymphoproliferative disease of recipient origin, often after reactivation of previously acquired Epstein-Barr (EBV) infection.[28] All the cases included in this study were of proven donor origin and diagnosed in the first 2 years after transplantation. Indeed, in 62% of cases donor origin was established with molecular techniques clearly reported, whereas in the other 38% an epidemiological criterion was considered. Our study highlighted a median time to diagnosis of 7 months for lymphomas, and this is in line with present literature. In general, tumors arising after long intervals are regarded as DDC, but there is currently no established time limit to differentiate them.[9] These tumors came from younger donors and were limited to the graft once developing, in contrast with what is more frequently

encountered in lymphoproliferative disorders of host origin.[29] Therefore, such epidemiological considerations should be taken into account in the perspective of establishing updated guidelines both for management of donors with different characteristics and of recipients with different disease.[30]

To the best of our knowledge, this is the first systematic review of published data on transmitted cancer in liver transplant recipients. We provide insights on the distribution and prognosis of recipients with transmitted cancers, confirming the worse prognosis of some cancer types and suggesting some important time points for recipients' follow-up. The main limitation of this study resides in the nature of the primary studies, which are mainly case reports distributed over a wide time span. The lack of complete data could have affected the reported distribution of donors' and recipients' characteristics and the estimates of times to diagnosis and survival probabilities. Indeed, inconsistent reporting of the various items, highly variable follow-up times, and the low number of some cancer types precluded a reliable evaluation of potential confounders, and for this reason, the analysis had to be limited to few clear characteristics, such as age and sex of recipients, localization of tumor, and retransplant as reference treatment. Moreover, we could not address the issue that cancers with highest malignant potential were mostly metastatic, while lymphoma and colorectal cancers were localized. We were aware of this when considering the entire recipient population and trying to subgroup for the three most frequent tumors.

In conclusion, the present findings are similar to those of previous studies, but this more extensive study illuminated the importance of lymphomas, melanomas, and neuroendocrine tumors as the most frequently transmitted cancers in liver transplant recipients. Approximately 80% of cancer diagnoses were established in the first year after transplant. Melanomas and neuroendocrine cancers have the worst prognosis. Findings are comparable with those in literature but will be refined in light of new treatment options, emphasize the importance of preventing tumor transmission, and highlight how the localization of tumor to the graft is the most important factor affecting prognosis, allowing removal of the tumor by retransplantation.

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Figure Legends

FIG. 1. Search flow diagram. The diagram has been realized according to the template of the PRISMA flow diagram[15] available at the PRISMA website (www.prisma-statement.org).

FIG. 2. Time to cancer diagnosis from transplantation for all recipients.

FIG. 3. Overall survival for all recipients.

FIG. 4. Time to cancer diagnosis from transplantation for the most frequent cancers.

FIG. 5. Overall survival for recipients with the most frequent cancers.

Supporting FIG. S1. Quality assessment of cases.

TABLE 1. Characteristics of Donors by Cancer Type

		Lymphoma	Melanoma	Neuroendocrine	Glioblastoma Multiforme	Choriocarcinoma	Colorectal	Other	Total
Age	Number of donors, n (%)	30 (32.6)	8 (8.7)	8 (8.7)	5 (5.4)	5 (5.4)	5 (5.4)	31 (33.7)	92 (100)
	Age range, years (median)	15-71 (23)	42-55 (51.5)	22-77 (62)	14-48 (38)	26-36 (30)	58-79 (69)	1-81 (52)	1-81 (47.5)
	Mean age, years (SD)	29.5 (16.8)	50 (5.7)	55.8 (25.2)	34.5 (16.2)	31 (4.8)	69 (7.5)	50.3 (19.9)	45.6 (20.4)
Sex	Male, n (%)	10 (33.3)	1 (12.5)	3 (37.5)	1 (20)	0 (0)	3 (60)	12 (38.7)	30 (32.6)
	Female, n (%)	2 (6.7)	3 (37.5)	3 (37.5)	2 (40)	5 (100)	2 (40)	11 (35.5)	28 (30.4)
	NA, n (%)	18 (60)	4 (50)	2 (25)	2 (40)	0 (0)	0 (0)	8 (25.8)	34 (37)
Known history of cancer, n (%)		0 (0)	1 (12.5)	0 (0)	5 (62.5)	0 (0)	0 (0)	2 (25)	8 (8.7)

Abbreviations: NA, not available; SD, standard deviation.

TABLE 2. Characteristics of Recipients by Cancer Type

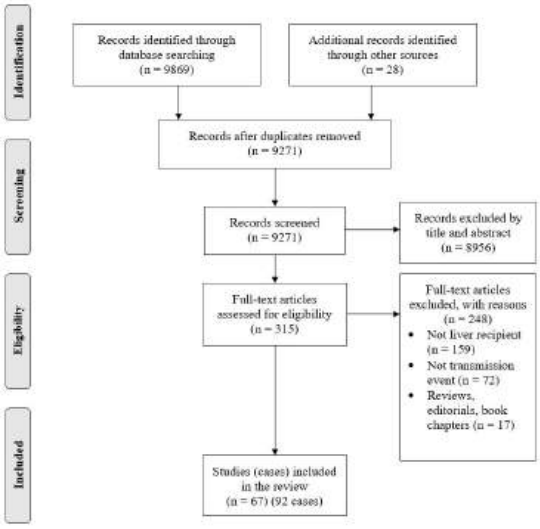
		Lymphoma	Melanoma	Neuroendocrine	Glioblastoma Multiforme	Choriocarcinoma	Colorectal	Other	Total
Age	Number of recipients, n (%)	30 (32.6)	8 (8.7)	8 (8.7)	5 (5.4)	5 (5.4)	5 (5.4)	31 (33.7)	92 (100)
	Age range, years (median)	18-62 (51.5)	35-62 (49.5)	33-60 (45)	14-29 (28)	18-64 (57)	53-66 (59)	1-73 (55)	1-73 (52)
	Mean age, years (SD)	48.4 (9.6)	47.5 (10.1)	47.2 (10.8)	23.7 (8.4)	46.3 (24.8)	59.6 (4.8)	51.6 (17.4)	49 (14.2)
Sex	Male, n (%)	23 (76.7)	4 (50)	5 (62.5)	0 (0)	1 (20)	4 (80)	16 (51.6)	53 (57.6)
	Female, n (%)	5 (16.6)	2 (25)	1 (12.5)	2 (40)	3 (60)	1 (20)	6 (19.4)	20 (21.7)
	NA, n (%)	2 (6.7)	2 (25)	2 (25)	3 (60)	1 (20)	0 (0)	9 (29)	19 (20.7)
Localization	Graft	25 (83.3)	1 (12.5)	2 (25)	1 (20)	0 (0)	5 (100)	12 (38.7)	46 (50)
	Metastasizing	1 (3.3)	5 (62.5)	4 (50)	4 (80)	5 (100)	0 (0)	10 (32.3)	29 (31.5)
	NA	4 (13.3)	2 (25)	2 (25)	0 (0)	0 (0)	0 (0)	9 (29)	17 (18.5)

Abbreviations: NA, not available; SD, standard deviation.

TABLE 3. Results of Survival Analysis

Variable	Univariable analysis		Multivariable analysis	
	HR (CI)	***P* value**	**HR (CI)**	***P* value**
Gender	1.70 (0.77-3.75)	0.19	1.11 (0.45-2.74)	0.82
Age	1.86 (0.89-3.88)	0.10	2.10 (0.84-5.32)	0.11
Localization	13.58 (4.61-40.04)	< 0.0001	12.56 (3.85-40.97)	< 0.0001
Treatment other than retransplant	2.14 (0.86-5.59)	0.10	2.72 (0.95-7.73)	0.06
Subgroup of most frequent cancers (lymphoma, melanoma, neuroendocrine cancer)				
Gender	1.35 (0.36-5.01)	0.65	-	
Age	0.97 (0.93-1.02)	0.19	0.97 (0.91-1.04)	0.37
Localization	14.89 (3.15-70.40)	0.0007	4.15 (0.19-92.34)	0.37
Treatment other than retransplant	1.23 (0.25-6.10)	0.80	-	
Diagnosis of melanoma (lymphoma as reference)	18.12 (4.38-75.07)	< 0.0001	6.20 (0.16-248.01)	0.33
Diagnosis of neuroendocrine cancer (lymphoma as reference)	4.79 (1.19-19.32)	0.03	11.06 (0.17-711.42)	0.25

Abbreviations: CI, confidence interval; HR, hazard ratio.



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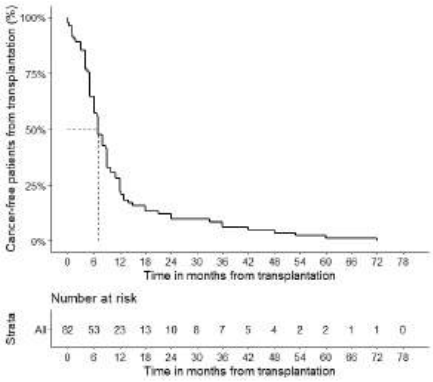

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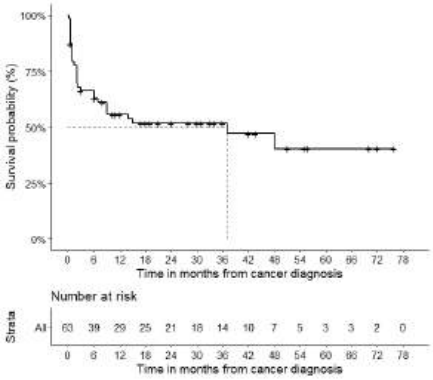

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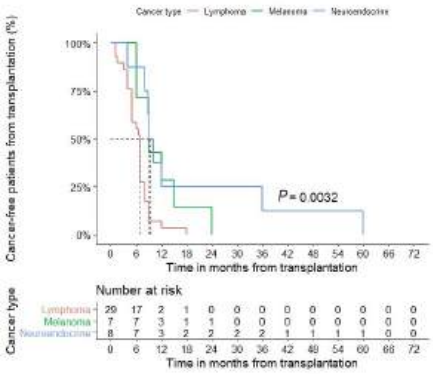

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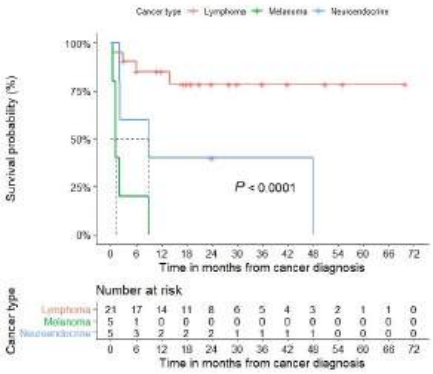

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