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Transplantation of liver and kidney from donors with malignancy at the time of donation: an experience from a single centre

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Summary

Transplantation of organs from donors with malignancy poses clinical and ethical questions regarding outcome, informed consent, immunosuppression and follow-up. We review our experience of kidney and liver transplantation from such donors. Our database was complemented by data from National Health Service Blood and Transplant. All patients who received a renal or liver transplant in our institution between April 2003 and January 2014 were included. About 2546 liver and kidney transplants were performed: 71 recipients received 53 kidney and 18 liver transplants. These included 51 (36 kidney, 15 liver) CNS malignancy, and six kidneys, three ipsilateral and three contralateral with RCC. One kidney recipient developed donor-transmitted lung cancer in the transplant kidney, and one liver transplant recipient developed donor-transmitted lymphoma; both subsequently died. Seven recipients developed donor-unrelated cancer. No recipient developed cancer, whereas the donor had a CNS or RCC. The 1-, 3- and 5-year patient survival was 96%, 93.3% and 75%, respectively, for kidneys and 83.3%, 75% and 50%, respectively, for liver. Where donor malignancy was known and assessed before transplantation, judicious use of kidney and liver for transplant achieved satisfactory outcome. The risk of transmission from donors with CNS and low-grade renal malignancy remains extremely low.

Introduction

Transplantation is the treatment of choice in patients with end-stage renal and liver disease. The risk of transmission of malignancy and infections is unavoidable in some cases [1–3]. Given the time-limited nature of deceased donation and the ethical restrains, thorough assessment of the donor for the absence of malignancy is not possible. The increasing age of the donor pool may also increase the risk of previously undiscovered malignancy in the donor. Nevertheless, the incidence of transmission of malignancy remains extremely low [4]. Past history of cancer in the donor does not always constitute an absolute contraindication, and organs may be used after a 'safe' disease-free period in the potential donor. This 'safe' period is variable and depends upon the type, grade and stage of the tumour. A detailed guideline for different tumour type and feasibility of transplantation is available from Israel Penn International Transplant Tumour Registry (IPTTR). Metastatic cancers are considered absolute contraindication. Cancer of upper gastrointestinal (GI) tract, pancreas, melanotic skin cancer, lymphomas and high-grade central nervous system (CNS) malignancy are considered 'unsafe'. However, registration in the IPTTR is voluntary and since its introduction, two further guidelines have been published: the Council of Europe Guidelines in 2010 [5] and UNOS [6] guidelines stating their recommendations on what is and is not acceptable for donor malignancy. The Notify Library

Project [7] has a database of adverse transplant outcomes including donor-transmitted cancer (DTC) that is accessible by the general public. Presence of active cancer at the time of donation is also considered contraindications with the exception of nonmelanotic, nonmetastatic skin cancers and low-grade (WHO grade I and II) CNS malignancy with no history of intervention or surgery. Kidneys with small renal cell cancer (RCC) have also been successfully transplanted after excision of the primary tumour [8] Often CNS malignancy is present as intracranial bleed, and the diagnosis may not be available at the time of donation. A prevalence rate of up to 2.7% CNS tumour has been described in hospital autopsy series [9]. Autopsy series of patients with intracranial malignancy have reported up to 0.5% incidence of metastasis for high-grade astrocytomas in adults [10] and up to 5% for medulloblastoma in children with predominantly bone, liver and lung metastases [11]. There have been a few case reports published recently, highlighting the risk of tumour transmission especially in donors with high-grade intracranial malignancies [12] and melanomas. Existing publications regarding intracranial malignancy have conflicting outcome, with some national registries showing no risk of transmission [3,13,14] while others demonstrating transmission [15,16]. The shortage of organs for transplantation has led to innovative strategies and increasing acceptance of high-risk donors. In the absence of uniform evidence-based guidelines for the use of an organ from donors with malignancy, such decisions are predominantly based upon the physician's knowledge and experience and evidence based upon case reports and small series.

This study aimed to analyse our institutional experience with the use of liver and kidney grafts from donors with a history of malignancy at the time of donation.

Methods

A prospectively maintained database of donors with malignancy and their organ recipients was scrutinized. This was supplemented with data obtained from National Health Service Blood and Transplant and missing data included in the study. To ensure completeness, the recipient and donor files of all 2546 recipients of liver or kidney transplant between April 2003 and January 2014 were reviewed by the authors to ensure robustness.

Follow-up of recipients was reviewed through the local results database and local clinical document and results system – specifically for any identification of subsequent cancer development. For recipients who were followed up in other centres, they were contacted for patient follow-up with specific reference to any cancer development.

The Regional Cancer Registry was cross-checked to identify recipient cancer development. Diagnosis of malignancy was made on histology in donors prior to organ recovery and in those with radiological diagnosis; confirmation of this diagnosis was obtained at autopsy postorgan recovery. All patients were followed up until January 2015.

Survival data analysis was calculated using SPSS v22 (IBM Corp 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY, USA:IBM Corp).

Results

About 2546 liver and kidney transplants were performed in the study period. Seventy-one recipients received 53 kidney and 18 liver transplants from donors with malignancy. This included 51 grafts (36 kidneys, 15 liver) from 43 donors with CNS malignancy and 20 grafts (3 livers, 17 kidneys) from 18 donors with non-CNS malignancies (Table 1). The median recipient age was 48.5 years (range 3–71) for kidneys and 53.5 years (range 21–62) for livers ($P = 0.766$). All 18 liver grafts were from DBD donors. About 41 of the renal grafts were from DBD and 11 from DCD donors. There was one live kidney donation. Those receiving organs from donors with CNS tumours were younger (mean age 41.5 vs. 54 $P = 0.002$). There was no difference between indication neither for transplant nor in any other comorbidity between the groups.

The type of malignancy and the recipients receiving these organs are summarized in Table 1. The grading of CNS malignancy is summarized in Table 2. Sixteen donors in the renal transplantation group and 10 donors in the liver transplant group had a history of intervention (14 renal and nine liver donors had craniotomy, two renal and one liver donor had biopsy, three renal and one liver donor had ventriculoperitoneal shunt, and three renal and one liver had a combination of these) for their CNS tumours prior to donation. Fourteen renal donors and nine liver donors received intervention within the week prior to donation. The cause of death in these cases was postoperative bleeding. The remaining three donors' intervention was between 1 and 5 years since the intervention: two were donors with pituitary tumours, and one was a donor with schwannoma. About four donors (three kidney and one liver) had received chemotherapy or radiotherapy or both, all >6 months predonation.

In 83% of recipients, the malignancy was known before transplantation. The remaining were identified after procurement of donor organs (the majority being kidneys) on back-table preparation, donor autopsy, unsuspected diagnosis upon biopsy of the donor organ or following occurrence of cancer in the recipient. All CNS tumours were known at the time of accepting the organ, though in some, information on the grade of the tumour became available after implantation.

Table 1. Type of donor malignancies in the recipients of kidney and liver transplant and the rate of transmission of malignancy.

Donor malignancy	Renal transplant recipients	Liver transplant recipients	Active Cancer at time of donation	History of treated cancer at time of donation	Diagnosis known before procurement	Diagnosis discovered after procurement and before implant	Diagnosis unknown until post- transplant	Tumour transmission
CNS	36	15	49	2	51	0	0	0
Renal	6	0	6	0	1	4	1	0
Breast	2	0	0	2	2	0	0	0
Cervical	2	0	0	2	2	0	0	0
Lymphoma	3	1	4	0	0	0	4	1 (liver recipient)
Lung	1	0	1	0	0	0	1	1 (renal recipient)
Atrial Myxoma	1	0	0	1	1	0	0	0
Papillary Thyroid	1	0	0	1	1	0	0	0
Liposarcoma	1	0	0	1	1	0	0	0
Gallbladder	0	1	1	0	0	0	1	0
Melanoma	0	1	1	0	0	0	1	0

Table 2. The types and the grades of CNS neoplasms in the donors of liver and kidney transplant.

	Grade I	Grade II	Grade III	Grade IV
Glioblastoma	0	3	1	9
Ependyoma	0	2	1	0
Neurocytoma	0	1	0	0
Astrocytoma	4	3	1	0
Pituitary	1 (macroadenoma)		1 (gonadotropinoma)	
Glioma	4		3	
Oligodendroglioma	0	2	2	0
Schwannoma	1	0	0	0
Meningioma	3 (grade unstated)			
Haemangioblastoma	1 (grade unstated)			

Different immunosuppression regimens were used during the study period for kidney and liver transplant. Between 2003 and 2009, renal transplant recipients received methylprednisolone and basiliximab induction followed by maintenance tacrolimus, mycophenolate mofetil (MMF) and prednisolone. From 2009, methylprednisolone induction and alemtuzumab induction were used followed by tacrolimus alone or tacrolimus, MMF +/−prednisolone in high immunologic patients. Basiliximab was used when donor malignancy was known. Sirolimus was substituted for tacrolimus in some, but not routinely for those who received organs from donors with cancer. Tacrolimus trough levels in both regimens were 9–14 ng/ml in the first 3 months followed by 5–9 ng/ml.

Liver transplant immunosuppression was tacrolimus, MMF and prednisolone for the entire study duration. Basiliximab induction was used in cases with evidence of acute kidney injury or chronic renal dysfunction. Cyclosporine A was used for hepatitis C early post-transplant. The tacrolimus trough levels were 4–9 ng/ml.

No recipients had developed cancer at the time of last follow-up where the diagnosis of cancer was known and assessed pretransplant (Table 3).

Follow-up in clinic was with the same regularity as other transplant recipients in our centre.

For the recipients who developed DTC, the cancer diagnosis was not known at the time of transplant. One recipient developed donor-transmitted lung cancer in the transplant kidney after 2 years and subsequently died 3 1/2 years post-transplant. The diagnosis was confirmed by DNA microsatellite array and tumour cells karyotyping (female donor, male recipient), both confirming tumour cells to be DTC. The paired kidney and the liver from the same donor were also transplanted. Neither recipient developed malignancy; the paired kidney was removed after a year for graft failure. The liver patient was lost to follow-up 8 years post-transplant with no malignancy at last follow-up. One liver transplant recipient developed donor-transmitted lymphoma (unsuspected from a lymph node biopsy at procurement and known only post-transplantation) after a period of 18 months and subsequently died 2 years post-transplant. This was confirmed by microsatellite array karyotyping (donor female and recipient male) on the tissue from a biopsied lymph node. One kidney from the same donor was also transplanted. This recipient died after 2 years with a functioning graft due to unrelated causes. The paired kidney from this donor was not used due to prolonged cold ischaemia time. One liver transplant recipient with incidental donor gallbladder cancer had a retransplant 2 days after their implant due to primary nonfunction and subsequently died the same day due to unrelated causes.

Seven recipients developed donor unrelated cancer: three skin, two lymphomas, one pancreas, one parotid, one nephroureteric transitional cell carcinoma of a native kidney and one cholangiocarcinoma.

Table 3. Transplantation of kidney with cancer.

Donor age	Recipient age	Diagnosis	Stage	Laterality	Follow-up (months)	Outcome
52	48	Oncocytoma	Fuhrman 1	Contralateral	63	Deceased, unrelated
65	41	RCC	Fuhrman 1	Contralateral	24	Working, no recurrence
47	3	RCC	Fuhrman 1	Ipsilateral	51	Removed on patients request
63	63	RCC	Fuhrman 1	Ipsilateral	12	Working, no recurrence
65	56	RCC	Fuhrman 1	Contralateral	25	Working, no recurrence
61	54	RCC	Fuhrman 1	Ipsilateral	35	Working, no recurrence

This study looked at the donors with a known history of malignancy at the time of donation. These were all early non-CNS malignancies, had received treatment with a range of 'disease-free' periods that were considered safe for donation. The two cases of donors with breast cancer were both DCIS diagnosed more than 10 years before donation, with complete excision and no history of disease recurrence or metastasis. Two donors had cervical intra-epithelial neoplasia (CIN III), 12 and 14 years before donation with complete excision and no subsequent progression. One donor had an early thyroid papillary cancer that was excised completely 15 years prior to donation. These cases were deemed by the transplant team at the time to be historical, and the donor could be considered as disease free. One recipient received a liver from a donor with a history of melanoma excised several years prior to donation. This was not known until post-transplantation of the liver. The recipient remains disease free. As mentioned before, in cases of donors with lung cancer, gallbladder cancer, melanoma and lymphoma, the diagnosis was not known pre-transplant.

In this study, the overall 1-, 3- and 5-year graft survival was 96% ($n = 50$), 92.8% ($n = 42$), 89.6% ($n = 21$), respectively, for kidney and 93% ($n = 15$), 93% ($n = 12$) and 93% ($n = 8$), respectively, for liver (death censored). Patient survival at 1-, 3- and 5-year graft survival was 96% ($n = 52$), 93.3% ($n = 45$) and 75% ($n = 29$), respectively, for kidneys and 83.3% ($n = 18$), 75% ($n = 16$) and 50% ($n = 8$), respectively, for livers. Median follow-up was 3.6 years.

Discussions

Donor history of cancer with very few exceptions (low-grade CNS tumour with no history of intervention and nonmelanotic, nonmetastatic skin cancer) was once considered an absolute contraindication to organ donation. Shortage of organs and death on the waiting list has lead to expansion of the acceptance criteria. This includes donors with history of or diagnosis of malignancy. Recently, donor organs with early malignancy (e.g. RCC) have also been successfully transplanted with good outcome. Such a paradigm shift is also helped by advances in cancer treatment, increasing confidence in 'cure from cancer' following a period of disease-free survival and better understanding of cancer biology. Organs from donors with history of cancer, those with cancer (e.g. CNS tumours) and some organs with cancer (e.g. kidneys) may be safely used for transplantation. This large institutional review has shown that when the donor malignancy is known and assessed before transplant, the overall risk of DTC is extremely low.

Extra-cerebral metastases of all types of primary CNS tumours are rare, occurring in 0.2% of cases [17–19] but associated with very poor prognosis [20]. Glioma accounts for 70% of all primary CNS tumours, of which half are glioblastoma (grade IV). These are aggressive tumours with a median survival of 2–5 years from diagnosis despite treatment. Oligodendriglioma has better prognosis (median survival 3–12 years) [21]. Ependymomas make up 4% of adult intracranial tumours [22] and rarely metastasize out of the blood–brain barrier [23]. Neurocytomas are rare, but with a good prognosis [24].

Donors with CNS tumours were the largest group in this series (51/71 transplants). The data on risk of transmission of malignancy from donors with CNS tumours are conflicting. Buell and colleagues [16,25] from their data from the IPTTR have shown CNS tumour transmission rate of 23%. Several specific risk factors were also identified including high-grade tumours, ventriculoperitoneal/ventriculoatrial shunting, craniotomy and external radiation. In the presence of these risk factors, the transmission rate was 46%. The IPITTR registry, being an event-based registry, may have resulted in higher event incidences, and reporting of events may be over-represented in comparison with the entire population at risk. This could be because not all cases of CNS tumour-positive donor transplants are reported. In addition, there is an inherent over-reporting bias since they have traditionally been notified regarding the occurrence of a cancer following transplantation but not the cancer-free survival of recipients of organs from donors with intracranial cancer. Watson and colleagues [3] in a UK-based series of 179 donors with intracranial malignancy found no transmission. This study included all donors with CNS malignancy, 33 with high-grade tumour (WHO Grade III/IV), 23 with grade IV GBM and 9 with medulloblastoma. However, that study was unable to identify those with risk

factors linked to the risk of recurrence in the recipient (e.g. VP shunt, craniotomy, radiation, chemotherapy). The Organ Procurement and Transplant Network (OPTN) from the US have shown three cases of transmission of GBM from a single donor from 642 CNS tumours [26].

Recent guidance from the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) transplants in the UK after extrapolating data from the UK National Transplant Registry has concluded that the overall risk of cancer transmission from deceased donors with a CNS tumour is 1.5% [27]. For high-grade tumours (e.g. glioblastoma), the risk has been estimated to be around 2.2%. The presence of a cerebrospinal fluid shunt may increase the risk of extra-neural metastasis, but this is estimated to be less than 1%. The recently published UK experience of DTC again did not show any transmission of CNS tumours to the recipients [14]. Based on these results, recommendations were formulated to provide guidance on use of organs from donors with CNS malignancy [27]. No transmission has been recorded from donors with CNS malignancy since the publication of Watson and colleagues in 2010 [3]. It can be extrapolated therefore that the risk of transmission is lower than that estimated earlier. This was confirmed in a recent publication from the same group [28]. The study by Desai and colleagues excluded any cancer diagnosis on the day or after recovery of organs. Equally, some postdonation cancer diagnosis may not have made it to the registry, therefore potentially excluding a significant number of donor cancer and some donor-transmitted malignancy from analysis. Such a problem is inherent in registry data, which has been obviated by our study.

In our series, 18 of 43 donors had high-grade malignancy, 21 had low grade and in 4, grade could not be determined. Many donors had one or more intervention (surgery, biopsy, VP shunt and/or external radiation). There was no tumour transmission including from those donors with risk factors. It should be noted that many (but not all) patients included in our study would have been included in the in the UK study with certain caveats. The final grades of some CNS tumours were different to that given at the time of donation, and this information became available days, or sometime weeks, post-transplant. This is reflected in our study. Diagnosis of some non-CNS tumours, for example renal cancer, was made after the procurement of organs, usually during back-table preparation. These would not always reflect accurately in the national data due to reporting inconsistencies. Where a kidney was discarded due to renal cancer or transplanted after excising small tumour, the fate of the paired kidney or other organ was not reported in the UK study. Our study addresses these issues. Finally, we feel that the follow-up data from a single centre to be more robust in its accuracy.

Donors with primary RCC formed a significant group in this series. Some reports have suggested that small solitary and well-differentiated RCCs may be resected and the kidney used for transplant [29,30]. The risk, however, remains where a cancer is multifocal and/or bilateral at the time of diagnosis and a synchronous occult tumour is missed at the time of transplantation. The risk of multifocal and or bilateral RCC at the time of diagnosis is quoted to be 0.3% with a relative risk increase of 3.1 for those with one tumour to develop a metachronous contralateral cancer [31]. Some earlier publication have reported up to 4% multicentricity and up to 3% bilaterality at the time of diagnosis [32,33].

No cross-sectional imaging technique has been evaluated to date for the diagnosis of cancer in the donated (ischaemic) organ. Our centre routinely employs backbench ultrasound assessment of the kidney to exclude multifocal or a bilateral RCC. In this series, no local or systemic recurrence was noted in the patients who received a kidney graft after excising a stage I RCC ($n = 3$) and those who received the contralateral kidney ($n = 2$). In one case, the diagnosis of an RCC was made post-transplantation following unsuspected biopsy of a scarred area. Whilst the biopsy suggested complete excision of tumour and further treatment and surveillance was offered, the graft was removed upon patient's request. We currently use kidneys from donors with stage I RCC after wide excision of the tumour or partial nephrectomy following informed discussion with the recipient. We would also use the contralateral kidney from the same donor after careful examination and ultrasound examination.

Buell *et al.* [29] first reported in 1995 a series of successful kidney transplants after excising small RCC. This consisted of a collection of cases reported to IPTTR with variable but short follow-up duration. Subsequently, Nicol *et al.* [8] in 2008 reported the first series of 43 kidney transplants from living and deceased donors after excising small renal tumour (<3 cm). Most of these kidneys were used in older recipients with one cancer recurrence (after 9 years) and no cancer-related deaths after a mean follow-up of 32 months. Subsequent publication [30] on the same cohort of recipients showed comparable survival outcomes compared with routine living donation and a survival benefit over those who remained on dialysis.

Donors with non-CNS tumours include a myriad of cancers with variable transmission rates based upon the type, stage and grade of the tumour, treatment received and years of disease-free survival [27] (Table 2). Several recommendations have been published in the recent past using different classifications. The Council of Europe Guidelines [5] classify some donors as having an unacceptable risk, whereas the UNOS guidelines [6] follow a similar classification as the UK, defining donors with a high or lower risk of

tumour transmission. Nalesnik *et al.* [34] suggested six levels of tumour transmission risk from nil to high (>10%). For those donors with high risk, it was recommended that the use of organs from such donors should be discouraged except in rare and extreme circumstances. Data from the UK registry have shown that in this subgroup, at 10 years from transplantation, the additional survival benefit gained by transplanting organs from donors with unacceptable/high-risk cancer was 944 life-years (95% CI 851–1037) with an average survival of 7.1 years (95% CI 6.4–7.8) per recipient. Current SaBTO [35] guidelines from 2014 state the only contraindications are active metastatic or haematological malignancy and consider melanoma, breast, colon, ≥grade 2 kidney, sarcoma, small cell cancer (lung or neuroendocrine) or any lung malignancies as being high risk.

In our series, 20 patients received organs from donors with non-CNS malignancy, 12 of these were known before implantation and were considered during the decision making process. The remaining eight were discovered after implantation (four lymphoma, melanoma, lung, gallbladder): seven liver transplant recipients and one only after tumour occurrence in the recipient (non-small cell cancer (NSCLC) in a kidney transplant recipient. Two of these recipients developed donor-transmitted cancer (lymphoma and NSCLC) and subsequently died. The recipient of liver transplant with incidental (on post-transplantation histology review) donor gallbladder adenocarcinoma died after two days of unrelated causes due to their comorbidity after an urgent re-graft for primary nonfunction. Review of the donor history did not show any suggestion of this diagnosis; a CT performed by the donor hospital reported the gallbladder as having a normal appearance.

Incidental gallbladder cancer is found in ~0.2% of laparoscopic cholecystectomy specimens and therefore remains a low possibility that it may be identified in future donors [36]. The recipient of liver from donor with history of treated melanoma was alive and disease free 36 months post-transplant. All these organs would not normally have been transplanted had the donor malignancy been known in keeping with the local and national guidelines. In the overall context of the number of transplants performed, the risk of donor-transmitted or donor-derived malignancy remains extremely low. Proper risk assessment, recipient selection and informed discussion should make an integral part of consent before proceeding to transplant. As evident from our report, the benefit of transplant outweighs the small risk of disease recurrence in these cases.

Given the extremely low transmission risk, we feel routine surveillance programme for tumour recurrence is not required for recipients from organs from donors with CNS tumour. For non-CNS donor tumours, a sensible surveillance programme based on the type and stage of the tumour should be instituted. The median follow-up in the present series was 3.6 years. There is a small risk of metastatic or recurrent disease years or even decades after original cancer diagnosis, including RCC [38,39]; therefore, this study could not detect those who may develop DTC beyond this. However, we feel that, although future events cannot be prevented, the benefits gained from transplantation to the recipient in terms of quality of life and reduction of mortality and morbidity should not be underestimated, even if a delayed DTC was found at a later date. For transplanted donor kidneys with tumours and the contralateral kidney, the authors suggest 3 monthly ultrasound scans of transplant kidney and 6 monthly chest X-ray for up to 2 years.

Those receiving organs from donors with non-CNS tumours were older than those from CNS tumour donors. There was no systematic reason for their allocation to these organs. We do not feel therefore this difference will have had any impact on outcome.

The incidence of nondonor-related cancer in our series is 9.8%. This is lower than 15% reported in UK registry data [37]. However, our study's follow-up is shorter compared to their long-term follow-up (30 years).

Our study is the largest reported single-centre series of kidney and liver transplant from donors with malignancy known at the time of transplant. The study adds to the growing body of literature supporting the feasibility of using organs from donors with malignancy. The risk of transmission is extremely low in CNS tumours of all grades irrespective of prior intervention or radiotherapy. The risk of transmission is also low in many non-CNS tumours following curative treatment and after a disease-free interval. When considering these organs for transplant, the risk of cancer transmission should be weighed against the morbidity and mortality on the waiting list, and informed discussion with the patient being integral to the process.

Authorship

NA: conceptualized the study and maintained the departmental database and acquired missing data from NHSBT, reviewed the manuscript and edited and approved the final version, will be the corresponding author. DL: collected additional data from locally stored donor datasheet and cross-checked each recipient for the absence of malignancy at the time of the study, wrote the manuscript and revised incorporating suggestions made by other authors. SP: analysed the data, wrote the manuscript and revised incorporating suggestions made by other authors. RB, KM, MA and LH: reviewed the manuscript.

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