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Cardiac or cardiopulmonary transplantation in childhood cancer survivors: An increasing need?

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ABSTRACT

Childhood cancer patients now have an excellent survival rate. Anthracyclines and radiation have contributed to this success, unfortunately at a cost. Both modalities are cardiotoxic and in some cases this is fatal unless treated by cardiac transplantation. This population-based study investigates the requirement for transplantation, patient demographics and transplant outcomes.

Childhood cancer survivors requiring a subsequent cardiac or cardiopulmonary transplant were identified by record linkage between the National Registry Childhood Tumours (NRCT) and United Kingdom Transplant registry (UKT). The clinical details were obtained from the treatment centres for confirmed matches.

Forty-three patients were identified as requiring cardiac transplantation: 36 underwent transplantation, 4 died while waiting and 3 were removed from the list. Their childhood cancers included 21 haematopoietic and 22 solid tumours diagnosed at a median age of 3.00 years (range 0.11–13.92 years). All patients were treated with anthracyclines (210–750 mg/m^2) and 15 received cardiac radiation.

The median age at cardiac transplantation was 14.80 years (range 3.26–23.92 years) and actuarial survival for the 36 who underwent cardiac transplantation was 74% and 67% at 5 and 10 years, respectively.

A further three patients underwent heart/lung transplantation: all three died from transplant-related causes.

Cardiac transplantation is a realistic option for cancer survivors, with survival rates comparable with those of other cardiac recipients. This study demonstrates that, over three decades, there has been an increased requirement for cardiac transplantation among childhood cancer survivors. Future planning for long term survivors needs to take this into account.

1. Introduction

Effective cancer treatment is resulting in an ever increasing number of long term survivors. Anthracyclines and radiation involving the heart are a central part of the treatment in more than 60% of children treated for cancer. Both these modalities are known to cause cardiotoxicity and contribute to the long term morbidity and mortality of cancer survivors.[1,2] The most important risk factor is high cumulative anthracycline dose (greater than 300 mg/m^2)[3] so many protocols now give a max-

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imum of 300 mg/m^2. Unfortunately there still remains a hard core of malignancies which require higher anthracycline doses to effect a cure thus putting patients at risk. A minority of patients progress to end stage cardiac failure when the only effective treatment is cardiac transplantation.

Transplant centres have been reluctant to place patients with a history of malignant disease on the transplant list because of the theoretical risk of inducing relapse of the primary malignancy, increasing the risk of second malignant neoplasms and the interaction between immunosuppression-induced side-effects and other co-morbidities caused by the previous oncological treatment. Small studies over the last decade, including our own in 1994,[4] have shown good post transplant survival rates.

This study aims to identify the changes in demand for transplantation and to compare the outcome for these patients with that of the generality of cardiac transplant patients. Our findings will therefore inform future planning and resource allocation.

2. Methods

2.1. Patient population

Patients were included in the study if they had been treated for a childhood cancer in the United Kingdom and subsequently required a cardiac or cardiopulmonary transplant. The patients were identified by linking the records from the National Registry of Childhood Tumours (NRCT) and the United Kingdom Transplant (UKT) database. The NRCT is a population-based registry covering England, Wales, Scotland and, since 1993, Northern Ireland.[5] The registry includes nearly all children under the age of 15 diagnosed with malignant disease from 1962 onwards with good levels of completeness.[6] Anthracyclines were first used within chemotherapy protocols for treating childhood tumours in the early 1970s, this study therefore includes only the patients diagnosed after 1969.

The UKT database was established in 1984 and includes records of all the patients who have been registered as requiring heart or heart/lung transplantation. The patients on the transplant register fell into four categories: those who received a heart or heart/lung transplant, those who died while awaiting a transplantation, those removed from the list and those actively awaiting for transplantation.

Multi Centre Research Ethics Committee and Patient Information Advisory Group (PIAG) approvals were sought and obtained to undertake the study without seeking individual patient consent.

Probabilistic record linkage techniques based on comparing the names and dates of birth were used to identify which of the childhood cancer patients had required transplantation. Matches were validated using additional information held on the registers (e.g. NHS number, death date and postcode information) and further clinical information was obtained via oncology and transplant treatment centres. Basic statistical analyses were performed using SPSS.[7] Because of the small numbers involved, medians rather than means were calculated and non-parametric Mann–Whitney *U* tests were used to test for the differences between medians. Kaplan–Meier survival curves were derived and log rank tests were used to compare the different survival curves.

3. Results

The NRCT registered 52,313 relevant patients diagnosed between 1970 and 2005 and details of these individuals were linked to those of 3528 patients from the UKT database entered on the register between 1985 and 2006. Forty-six patients were identified and verified as fitting the study criteria. Of those 46, 3 underwent heart/lung transplantation and the remaining 43 required cardiac transplantation.

3.1. Heart/lung transplant patients

Three patients required combined heart and lung transplantation for end stage pulmonary disease. Two patients had been treated for relapsed acute lymphoblastic leukaemia with a regime including anthracyclines (225,380 mg/m^2), Total body irradiation (TBI) prior to allogenic bone marrow transplant (BMT). Both patients underwent transplantation between 5 and 6 years after completing oncology treatment and their pulmonary disease was due to graft versus host disease. The remaining patient was treated with surgery and thoracic radiation alone (30 Gy) at 2 years of age for ganglioneuroblastoma and underwent transplantation 15 years after completing oncology treatment.

All three patients died within 2 years of undergoing transplantation due to pulmonary sepsis.

3.2. Cardiac transplant patients

All the results that follow refer to the 43 patients who were listed for cardiac transplantation.

Twenty-two of the 43 patients were females and 21 were males. Their malignancies were diagnosed between 1973 and 2004. Twenty patients were treated for leukaemia (16 acute myeloblastic leukaemia (AML), 4 acute lymphoblastic leukaemia (ALL)) and one patient for non-Hodgkin lymphoma (NHL). The remaining 22 patients had all been treated for solid tumours including 7 Wilms' tumours (WT), 6 rhabdomyosarcoma, 2 each of osteosarcoma, neuroblastoma and hepatoblastoma and single cases of 'histiocytosis', Ewings sarcoma and testicular yolk sac tumour. The median age at diagnosis was 3.00 years (range 0.11–13.92 years).

All the patients received anthracyclines as part of their treatment (Fig. 1). Twenty-two patients received doxorubicin (dose range 225–680 mg/m^2), 17 patients received daunorubicin (dose range 210–570 mg/m^2) and 3 patients received epirubicin (dose range 450–750 mg/m^2). One patient received epirubicin (200 mg/m^2) in combination with daunorubicin (80 mg/m^2). Sixteen patients received cyclophosphamide in addition to anthracyclines, and the doses received ranged from 0.6 to 33.0 g/m^2 with 10 patients receiving less than 5.0 g/m^2. One patient received carnitine as a cardioprotector during relapsed treatment. Twenty-one patients received radiation; in 15 patients the field involved the heart – lung (1), Left flank (2), or both (3), thoracic spine/chest wall (4) and TBI (5).

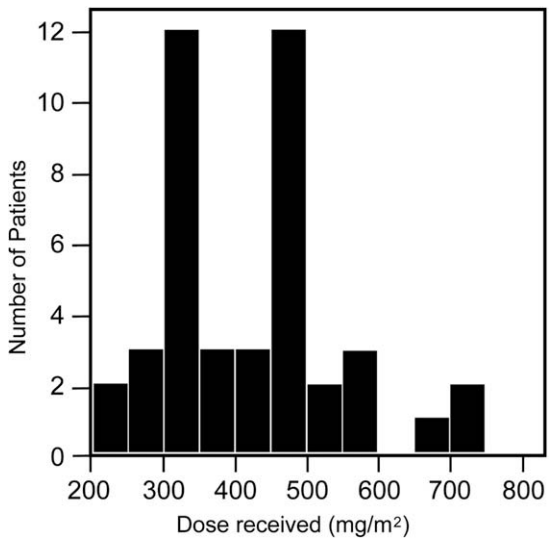

Fig. 1 – Anthracycline doses.

The largest diagnostic groups were the AML survivors who required transplantation between 1991 and 2006. Median age at diagnosis was 3.09 years (range 0.70–11.05 years). All AML patients received daunorubicin with a range 210–570 mg/m^2. Twelve received mitroxathrone and amascrine at standard doses (mitroxathrone 50 mg/m^2, amascrine 500 mg/m$^{2)}$, 1 received standard mitroxathrone dose but reduced amascrine dose (284 mg/m^2) and 1 received mitroxathrone 88 mg/m^2 with amascrine 376 mg/m^2 and cyclophosphamide. Three patients were treated with TBI. Three of the 16 AML patients had chromosomal abnormalities, two cases of Down syndrome Trisomy 21 and one of Klinefelter syndrome/46XXY.

Seven WT patients required transplantation. All the 7 had left-sided tumours and 6 were treated before 1984. The doxorubicin doses ranged between 320 and 500 mg/m^2 and 6 of the 7 received radiation to fields that would have included the heart (left flank and lung).

The patients were referred to the cardiologists with either reduced fractional shortening on echocardiography or clinical cardiac failure at a median time 2.30 years (range 0.00–16.94 years) from the end of oncology treatment. Seventeen presented with symptoms less than 12 months from the end of treatment.

Of the 43 patients listed for heart transplantation, 35 received a single heart transplant, 1 patient required a repeat transplant and 4 died while awaiting for transplantation. The remaining three patients were removed from the list, two because of improving heart function and one following a relapse of their primary tumour (AML). The cardiac transplantations were performed between 1984 and 2006 at a median age of 14.80 years (range 3.26–23.92 years). Five transplants were performed in the 1980s, 16 in the 1990s and 15 have been performed between 2000 and 2006.

The time from cancer diagnosis to requiring a cardiac transplant was significantly affected by the age of cancer treatment. Patients less than 5 years of age ($n = 29$) at cancer diagnosis were able to wait for significantly longer time before being listed for transplantation ($p < 0.01$) compared with the older children ($n = 11$) (Table 1). However, there was no significant difference in median age at transplantation between the two groups.

The group presenting with early onset (i.e. less than 1 year from end of oncology treatment) cardiac dysfunction ($n = 17$) were able to be managed conservatively for significantly longer time ($p < 0.05$) before requiring transplant listing: median 3.52 years (range 0.03–14.60 years) compared with 1.06 years (range 0.01–13.63 years) for the late onset group ($n = 21$). (No cardiac referral date was recorded for five patients.)

Although males ($n = 17$) were older at the time of transplantation with a median age of 16.12 years compared with that for the females ($n = 19$) 13.63 years, this difference was not significant.

Table 1 – Patient details.

	Time from end of cancer treatment to cardiac referral Median in years (range)	Time from end of cancer treatment to transplant listing Median in years (range)	Time from end of cancer treatment to transplant Median in years (range)	Age at transplant Median in years (range)
All patients, $n = 43$	2.30 (0.00–16.94), $n = 38$[a]	7.91 (0.48–17.34), $n = 40$	8.19 (0.55–17.49), $n = 36$	14.80 (3.26–23.92), $n = 36$
Age < 5 years $n = 31$	4.99* (0.02–16.94), $n = 29$	9.80** (0.48–17.34), $n = 29$	9.90** (1.04–17.49), $n = 27$	14.70 (3.26–23.92), $n = 27$
Age > 5 years, $n = 12$	0.32 (0.00–6.31), $n = 9$	3.10 (0.48–15.19), $n = 11$	3.59 (0.55–9.31), $n = 9$	15.17 (7.39–22.63), $n = 9$
Males, $n = 21$	1.93 (0.00–16.94), $n = 18$	9.47 (0.68–15.34), $n = 20$	9.81 (0.74–17.09), $n = 19$	16.12 (7.39–23.92), $n = 19$
Females, $n = 22$	2.73 (0.00–13.09), $n = 20$	7.30 (0.48–17.34), $n = 20$	8.10 (0.55–17.49), $n = 17$	13.63 (3.26–22.63), $n = 17$

* $p < 0.05$.
** $p < 0.01$.
a Differences in the number of patients arise because of missing information, e.g. date of cardiac referral not recorded for 5 patients.

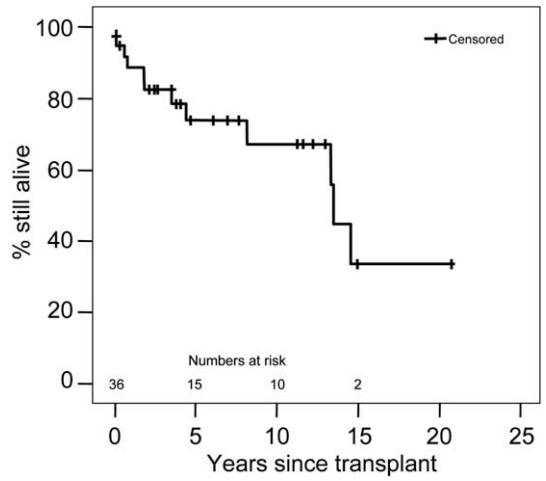

Fig. 2 – Actuarial survival after cardiac transplantation.

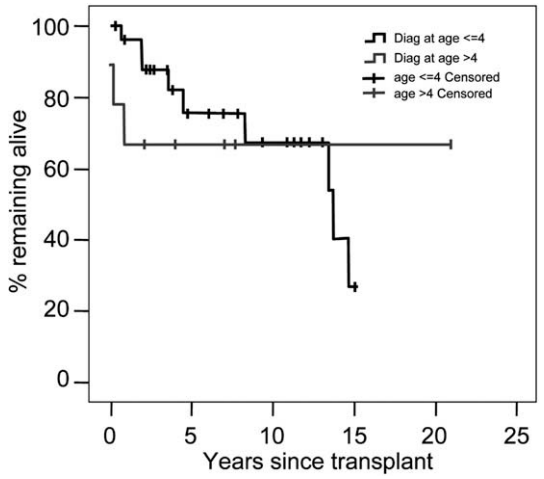

Fig. 4 – Actuarial survival for age at cancer diagnosis.

For the 36 patients who underwent cardiac transplantation, the actuarial survival was 74% and 67% at 5 and 10 years after transplantation, respectively, with survival ranging from 0.15 to 20.93 years (Fig. 2). Twelve patients died at a median time of 2.76 years (range 0.05–14.68 years) after transplantation.

The 5 year survival for those presenting with early onset cardiac disease ($n = 14$) was 59%, worse than that for the late onset group ($n = 19$) 85% ($p = 0.07$). This high survival rate in the late onset group was maintained at 10 years. The 7 post transplant deaths among the early onset group occurred earlier at a median time of 1.92 years from transplant (range 0.70–13.65 years) compared with 4 deaths among the late onset group at a median time of 8.92 years from transplant (range 0.24–14.68 years) (Fig. 3).

The age when cancer treatment was delivered made no difference to the outcome at 10 years (Fig. 4).

All 12 deaths were due to transplant-related causes, rejection (8), coronary artery disease (2), multi-organ failure (1) and 1 patient had an intracranial bleed associated with high Ebstein Barr viral load. Within the survivor group 2 patients with a primary diagnosis of AML relapsed 2 months and 4 years after transplantation and 1 patient was treated for immunosuppression-related B-cell lymphoma. Renal dysfunction was commented on 3 patients and 1 patient required a renal transplant.

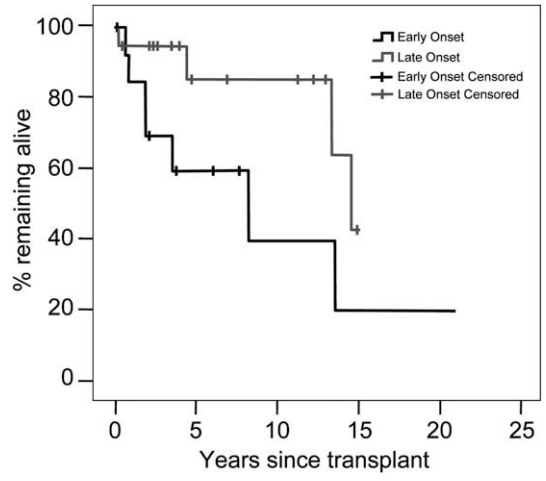

Fig. 3 – Actuarial survival for early and late onset cardiac disease.

4. Discussion

A third of paediatric cardiac transplantations are performed as definitive treatment for cardiomyopathy. Of those, only a minority (5%) are due to anthracycline-related cardiomyopathy.[8] On the other hand from a paediatric oncologist's perspective, cardiac disease in 5 year survivors of childhood cancer is the second commonest cause of late mortality, excluding relapse of the primary malignancy[1] and a significant proportion of the cardiac deaths are attributable to cardiomyopathy. By updating our population-based study of cardiac transplantation in childhood cancer survivors, we wished to determine if there had been a change in the patient demographics, outcomes or demand for transplantation.

The cases contributing to this study were all ascertained from existing registers thus avoiding selective recall bias. The registries used (NRCT, UKT) are both population based and thus able to provide a clear picture of the national need for transplantation among this patient group.

Anthracyclines were an integral part of the cancer treatment plan in all the patients with the majority receiving a dose greater than 300 mg/m$^{2.}$and over a third of patients treated with concomitant cardiac radiation. Since our previous study there has been a threefold increase in transplant requirement with an increase from decade to decade. There are a number of factors which may have contributed to this increase. Firstly more patients are at risk of cardiomyopathy as a consequence of improved survival rates. This is borne out by the change in the distribution of diagnostic groups presenting for transplantation between the series. AML survivors are now the predominant group (37%). The survival rates for

AML have improved three fold over the last 2 decades with the development of more intensive protocols involving high anthracycline doses (>300 mg/m^2).[5]

Secondly, a change in referral pattern may contribute to this increased demand. Awareness of long term cardiac morbidity has been highlighted and, internationally, long term follow-up guidance suggests regular surveillance of cardiac function for all patients receiving anthracyclines with early cardiac referral if deterioration of function noted.[9,10] This proactive surveillance may mean that the patients are referred early for cardiac transplant assessment thus reducing mortality before transplant listing. Equally as outcome evidence accumulates transplant centres are more likely to accept them.

In contrast, intensity of treatment has been reduced in tumours with a good prognosis. This has resulted in only one Wilms tumour survivor treated after 1984 requiring transplantation for early onset cardiac failure. Interestingly, all the Wilms tumour patients had left-sided tumours with five of the seven patients receiving left flank radiation either alone or in association with lung radiation. The cumulative cardiac dose for these may well have exceeded 25 Gy. Pein[11] showed there was an increased risk with radiation doses to the heart above 20 Gy. More recent treatment regimes have modified anthracycline doses to 300 mg/m^2 and increased care with radiation exposure to the heart by matching of lung and flank radiation fields.

A review of the literature on heart transplantation for childhood cancer survivors found 6 series from 1990 to 2004[12–17] (Table 2). Two were excluded from the table as in one[12] there was a potential overlap of patients with Ward's larger series[16] and the other[17] included childhood cancer survivors but details of the patients' ages at diagnosis were not given. The patients described in our earlier study[4] are all included in our current study with longer follow up where applicable.

The four listed studies together describe 30 patients. The major diagnostic groups were Ewings sarcoma (7), Wilms tumour (5), NHL (6), leukaemia (5) and Soft tissue sarcoma (4), all received anthracyclines and, where stated, doses were in the range 75–600 mg/m^2. Doses of anthracycline below 250 mg/m^2 were only recorded in 2 of 17 patients in Ward's study[16] whereas we identified 2 out of 43 patients receiving a low dose. These patients may exhibit a genetic susceptibility to anthracycline cardiotoxicity. Future work on gene polymorphism may enable identification of these patients prior to anthracycline treatment.[18]

The age at transplantation in the other studies was similar to that in our series (range 3.26–23.92 years). We found a non-significant difference in age at transplantation between the sexes, with females transplanted earlier compared to males. This may suggest that the combination of pubertal growth spurt and sex hormone production may precipitate irreversible heart failure.

In our study the overall 5 year survival has been excellent at 74%. Both the 5 and 10 year survivals are in line with international results for patients undergoing paediatric cardiac transplantation for all causes.[19]

Patients with a history of malignancy may be considered to be at increased risk of mortality due to the theoretical risk of relapse of the primary tumour, lymphoproliferative disease and second malignant neoplasms (SMN). This does not seem to be borne out in the available data. In our study only 2 of the 43 patients relapsed, both with AML. They received their cardiac transplants 9 months and 10 years from the end of their treatment and relapsed 2 months and 4 years post transplant. Both were successfully retreated with one patient receiving high dose treatment with a bone marrow rescue.[20] In the other studies, 1 of 30 Ewings sarcoma patients, transplanted more than 5 years from cancer treatment, was reported to have relapsed 15 months after cardiac transplantation. Lymphoproliferative disease was diagnosed in a single patient in our series and a fatal case was reported in Ward's group, giving similar rates to those from registry data.[21] No life threatening SMNs were reported.

Patients who were referred less than 12 months after the end of the treatment appeared to have a worse outcome. There is no obvious reason for this, but the criteria for cardiac referral appeared to vary enormously from asymptomatic patients with a fractional shortening (FS) of 27% to symptomatic patients with FS as low as 6%. The patients with early onset cardiac disease recorded FS lower than 20% but the referral FS did not predict outcome. Cancer treatment can damage other major organs and therefore may jeopardise the outlook for these patients but the treatment received prior to transplant did not seem to affect survival. In particular, those who received TBI (5), known to cause multi-organ morbidity,[22,23] all survived albeit with short follow-up. Overall, no deaths were reported to be related to co-morbidities.

The other consideration raised is the minimum time patients should be malignancy free before acceptance for transplantation. In a study of recurrence risk of Hodgkins disease and NHL after organ transplantation, Trofe et al.[24] suggested that those less than 2 years from diagnosis were at a greater risk of relapse. In our series 5 patients were listed for transplantation within 2 years of completion of treatment but only three were transplanted. All are alive and well but 1 (AML) relapsed as described above. In the other four series there are at least 4 patients transplanted within 12 months, one patient with Ewing's sarcoma relapsed at 15 months but was successfully retreated but died of a pulmonary embolus at 4.8 years post transplant. Encouragingly in our study, of the 17 patients with early onset cardiac dysfunction only 5 required to be listed for transplantation within 2 years of completing treatment: overall this group could be managed conservatively for longer time than the late onset group ($p < 0.05$). In Ward's study, 3 of 9 early onset patients required prompt transplantation.

In the United States (US) it is usual to be in complete remission for 5 years before listing for transplant, However, Ward et al.[16] have suggested that this be reconsidered as the outcome after transplantation is good and recurrence is rare and cannot be attributed to the post transplant drug administration. In the United Kingdom (UK), paediatric centres, in conjunction with oncologists, consider cases individually. Nevertheless, it is uncommon to list children for transplantation less than 2 years from completion of treatment. When referring patients for transplantation, the individual's risk of relapse and the scarcity of suitable organs need to be considered.

Table 2 – Literature review cardiac transplantation in childhood cancer survivors.

Study	Patients	Age at cancer diagnosis	Cancer diagnosis[a]	Anthracyclines (mg/m^2)	Cardiac RT	Time from cancer diagnosis to transplant	Age at transplant	Survival	Recurrence of primary malignancy
Edwards et al.[13] 1990 USA	3*	7, 9, 6 years	NHLx2, ALL	Doxorubicin 475,395, unknown dose	1	Disease free 4, 7, 4 years	12, 18, 19 years	2 Alive (4, 7 years FU) 1 Died 6 months post transplant	0
Musci et al.[14] 1997Germany	5	Median 1 year (range 0.75–15.0 years)	WTx2, EWS, ALL, STS	Doxorubicin mean 435 (range 185–600)	2	Mean 6 years (range 2–9 years)	Mean 15.6 years	No deaths FU 3.1–5.4 years	0
Grande et al.[15] 2002 Italy	5*	1–7 years	EWS,STS,WT, AML,CML	Doses not stated	Not stated	Mean 6.25 years (range 1.75–11.00 years)	Mean 15 years (range 10–25 years)	1 Death 1 day post transplant 4 Alive FU 2.6–15.8 years	0
Ward et al.[16] 2003 USA	17	Mean 6.0 years (range 1.5–11.9 years)	EWSx5, NHLx4, WTx2, STSx2, PNET, NBL, FIB, ALL	Mean 361 (range 75–540)	6	Mean 7.7 years (range 0.4–15.2 years)	Mean 13.9 years (range 6–18 years)	100% at 1 year 92% at 2 years 60% at 5 years	EWS 15 months post HT

* Paediatric cases were extracted from a larger series.

a EWS: Ewings sarcoma, STS: soft tissue sarcoma, PNET: Peripheral neuroectodermal tumour, NHL: Non-Hodgkins lymphoma, OS: osteosarcoma, WT: Wilms tumour, ALL: Acute lymphoblastic leukaemia, AML: Acute myeloblastic leukaemia, CML: Chronic myeloid leukaemia, NBL: Neuroblastoma, FIB: Musculoaponeurotic fibromatosis

Heart and lung transplant recipients fared poorly in our study, all died within 2 years of transplant from pulmonary infections. No new heart/lung transplants have been performed since 2000 but this study does not address the issue of lung only transplantation.

In conclusion, our population-based study identifies a need for cardiac transplantation in survivors of childhood cancer treatment. This requirement appears to be growing as long term survival improves. There is no evidence to suggest that these patients should be excluded from transplant programmes as both our study and others show good overall survival.

Conflict of interest statement

None declared.

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Transplant centres: Freeman Hospital Newcastle – Dr. Richard Kirk, Miss Angela Nicholson; Great Ormond Street Hospital for Children Dr. Joshua Simmonds, Sister Nadine Shaw;Harefield Hospital – Sister Josephine Archer, Dr. Uldershaw, Dr. Franklin.

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