# Solid organ transplantation after treatment for childhood cancer: a retrospective cohort analysis from the Childhood Cancer Survivor Study

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## Summary

**Background** Serious chronic medical conditions occur in childhood cancer survivors. We aimed to investigate incidence of and risk factors for end-organ damage resulting in registration on a waiting list for or receiving a solid organ transplantation and 5-year survival following these procedures.

**Methods** The Childhood Cancer Survivor Study (CCSS) is a retrospective cohort of individuals who survived at least 5 years after childhood cancer diagnosed at younger than 21 years of age, between Jan 1, 1970, and Dec 31, 1986, at one of 25 institutions in the USA. We linked data from CCSS participants treated in the USA diagnosed between Jan 1, 1970, and Dec 31, 1986 (without solid organ transplantation before cohort entry) to the Organ Procurement and Transplantation Network—a database of all US organ transplants. Eligible participants had been diagnosed with leukaemia, lymphoma, malignant CNS tumours, neuroblastoma, Wilms' tumours, and bone and soft tissue sarcomas. The two primary endpoints for each type of organ transplant were date of first registration of a transplant candidate on the waiting list for an organ and the date of the first transplant received. We also calculated the cumulative incidence of being placed on a waiting list or receiving a solid organ transplantation, hazard ratios (HRs) for identified risk factors, and 5-year survival following transplantation.

**Findings** Of 13 318 eligible survivors, 100 had 103 solid organ transplantations (50 kidney, 37 heart, nine liver, seven lung) and 67 were registered on a waiting list without receiving a transplant (21 kidney, 25 heart, 15 liver, six lung). At 35 years after cancer diagnosis, the cumulative incidence of transplantation or being on a waiting list was 0·54% (95% CI 0·40–0·67) for kidney transplantation, 0·49% (0·36–0·62) for heart, 0·19% (0·10–0·27) for liver, and 0·10% (0·04–0·16) for lung. Risk factors for kidney transplantation were unilateral nephrectomy (HR 4·2, 95% CI 2·3–7·7), ifosfamide (24·9, 7·4–83·5), total body irradiation (6·9, 2·3–21·1), and mean kidney radiation of greater than 15 Gy (>15–20 Gy, 3·6 [1·5–8·5]; >20 Gy 4·6 [1·1–19·6]); for heart transplantation, anthracycline and mean heart radiation of greater than 20 Gy (dose-dependent, both p<0·0001); for liver transplantation, dactinomycin (3·8, 1·3–11·3) and methotrexate (3·3, 1·0–10·2); for lung transplantation, carmustine (12·3, 3·1–48·9) and mean lung radiation of greater than 10 Gy (15·6, 2·6–92·7). 5-year overall survival after solid organ transplantation was 93·5% (95% CI 81·0–97·9) for kidney transplantation, 80·6% (63·6–90·3) for heart, 27·8% (4·4–59·1) for liver, and 34·3% (4·8–68·6) for lung.

**Interpretation** Solid organ transplantation is uncommon in ageing childhood cancer survivors. Organ-specific exposures were associated with increased solid organ transplantation incidence. Survival outcomes showed that solid organ transplantation should be considered for 5-year childhood cancer survivors with severe end-organ failure.

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## Introduction

More than 80% of children diagnosed with malignancy who receive treatment will become long-term survivors.[1] However, increased risks of long-term morbidity and premature mortality from renal, cardiac, hepatic, pulmonary, and other medical conditions are well established as this population ages.[2–7] We previously reported that by 20 years following cancer diagnosis, the cumulative incidence of severe, disabling, or life-threatening conditions or death due to chronic conditions was 27·5% (95% CI 26·4–28·6) among survivors diagnosed from 1990 to 1999.[8] Another study showed that when childhood cancer survivors age 45 years were clinically evaluated for serious, disabling, or life-threatening conditions, the cumulative prevalence of these conditions was 80·5% (95% CI 73·0–86·6).[9]

The crude prevalence of long-term adverse health outcomes associated with specific organs in childhood cancer survivors has been described as follows: 65·2% (95% CI 60·4–69·8) for abnormal pulmonary function,

## Research in context

### Evidence before this study

We searched PubMed for literature published in the English language from Jan 1, 1966 up until Jan 1, 2019, with the search terms "pediatric cancer survivors" and "liver transplantation", "kidney transplantation", "lung transplantation", or "heart transplantation", or a combination of all four. We subsequently examined the bibliographies of references gathered. Most of the literature found consisted of case reports and small case series that were descriptive in nature, without detail regarding risk factors or group summary statistics.

### Added value of this study

This study is the first to link the Childhood Cancer Survivor Study population, the largest North American cohort of paediatric cancer survivors, with the Organ Procurement and Transplantation Network, representing all solid organ transplants done in the USA. To the best of our knowledge, this study is the largest analysis to date to define the incidence of, risk factors for, and survival after end-organ failure and transplantation in survivors of childhood cancer, enabling providers and patients to better understand risks after cancer therapy as well as survival after this potentially life-saving intervention.

### Implications of all the available evidence

This study will help inform health-care providers about the risk of life-threatening solid organ failure and benefits of transplantation after diagnosis and treatment of common paediatric cancers. It provides evidence for efficacy of organ transplantation in recipients with a history of paediatric cancer, informing practice in the organ transplant subspecialties. Additionally, it provides data for third-party payers who might be resistant to pay for these rare, life-saving procedures after a paediatric cancer diagnosis, on the basis of old and scarce reports published in the literature.

56·4% (53·5–59·2) for cardiac conditions, 13·0% (10·8–15·3) for liver dysfunction, and 5·0% (4·0–6·3) for kidney dysfunction, at a median age of 25.1 years from diagnosis (range 10·9–47·9).[9] However, these reports do not adequately emphasise the prevalence of end-organ failure sufficient to require therapeutic intervention in this population. Solid organ transplantation is a therapeutic option for end-organ failure resulting from childhood cancer therapy.[2,10–12] Only case reports of a small number of cancer survivors undergoing kidney, heart, liver, or lung transplantation are available.[10,12–16]

The Childhood Cancer Survivor Study (CCSS) is a retrospective cohort study of children who have survived childhood cancer diagnosed at least 5 years previously. The cohort includes patients diagnosed between 1970 and 1986, who were younger than 21 years at diagnosis, recruited from one of 25 institutions in the USA (appendix p 1). The Organ Procurement and Transplantation Network (OPTN), which is administered by the United Network for Organ Sharing (UNOS) in contract with the US Health Resources and Services Administration, actively tracks occurrence and outcomes of more than 30 000 solid organ transplantations each year in the USA. The OPTN website notes that more than 400 abstracts and manuscripts relating to, or based on, OPTN data have been published. These two large databases, each a unique resource with a wealth of information, have never previously been linked. The OPTN has been linked to other large databases for studies in organ transplantation,[17] but the only similar linkage between two large databases comparable to this study occurred with the National Wilms Tumor Study and the United States Renal Data System to look at end-stage renal disease in survivors of Wilms' tumour, inclusive of kidney transplantation.[2]

Incidence of, risk factors for, and long-term outcomes following solid organ transplantation in childhood cancer survivors are unknown. This study aimed to establish the first data linkage between CCSS and OPTN to identify and describe outcomes in a large population of childhood cancer survivors who subsequently underwent kidney, heart, liver, or lung transplantation. Knowledge of survival following solid organ transplantation will provide evidence to health-care providers and survivors regarding the consideration of solid organ transplantation in this population.

## Methods

### Study design and participants

The CCSS—a retrospective, cohort study—includes individuals who have survived childhood cancer diagnosed at least 5 years previously who were diagnosed at younger than 21 years of age, between Jan 1, 1970, and Dec 31, 1986, with leukaemia, lymphoma, malignant CNS tumours, neuroblastoma, Wilms' tumours, or bone and soft tissue sarcomas. This cohort has been previously well described.[18] Survivors with other tumours, including hepatoblastoma, retinoblastoma, and germ cell tumours, were not eligible for CCSS. For this analysis, eligible participants were childhood cancer survivors in the CCSS cohort who were not from Canada and who did not have a solid organ transplant before entry into CCSS. Participants could be either English or Spanish speaking. Participants provided written informed consent, and all institutions obtained institutional review board approval for CCSS.

Dates of death and causes of death were ascertained for the CCSS cohort via matching with the US National Death Index, with deaths through Dec 30, 2013, available for this analysis. The CCSS is an approved user of the US National Death Index.

For more on the **Childhood Cancer Survivor Study** see http://ccss.stjude.org

See **Online** for appendix

For more on the **Organ Procurement and Transplantation Network** see http://optn.transplant.hrsa.gov

## Procedures

After informed consent was obtained, all participants (or their proxy) completed a baseline questionnaire, with questions about demographic data, medical conditions, surgeries, medications, and social and family histories. All participants still surviving received follow-up questionnaires in 2000, 2003, 2005, and 2007. Data on treatment received at the local participating centres, including chemotherapy, surgery, and radiotherapy, were systematically abstracted from medical records of survivors who authorised release via local, trained study personnel.[18] No additional abstraction was done for this current study. All CCSS questionnaires are available online.

For the **CCSS questionnaires** see https://ccss.stjude.org/tools-and-documents/questionnaires.html

For more on the **OPTN** see https://optn.transplant.hrsa.gov/data/about-data/

The online database system for the OPTN launched on Oct 25, 1999, and contains data regarding every organ donation and transplant event occurring in the USA since Oct 1, 1987. We determined the occurrence of solid organ transplantation by obtaining data from the OPTN, with or without corresponding CCSS data, after Oct 1, 1987. For solid organ transplantation that had occurred before OPTN inception, the transplantation was determined by self-report on a questionnaire or medical record abstraction. The OPTN data system includes data on all donors, candidates on waiting lists, and transplant recipients in the USA, submitted by the members of the OPTN, and is overseen by the US Department of Health and Human Services.

Through a data-sharing agreement with OPTN, solid organ transplantations and waiting list outcomes were obtained for all eligible CCSS participants up to Dec 31, 2013. This analysis only used data from individuals in the CCSS cohort with solid organ transplantation who were verified via linkage to a record in the OPTN database, on the basis of matching name, sex, date of birth, and, if available, social security number. All matches were reviewed by ACD, KS, WML, and AMT for additional agreement between available clinical data. Further detail on the methods for linkage between CCSS and OPTN is provided (appendix pp 2–3).

## Outcomes

The objectives of this study were to determine the incidence of being placed on the waiting list for, or receiving, a kidney, heart, liver, or lung transplant in eligible CCSS patients; to determine associations between cancer treatment received in childhood and organ damage severe enough to warrant eligibility for solid organ transplantation; and to identify the 5-year survival of CCSS participants following solid organ transplantation. The two primary endpoints were date of first registration of a transplant candidate on the waiting list for an organ, and the date of the first transplant received. For individuals who were not placed on a waiting list before receiving a transplant, the date of transplant was utilised as their event time for waiting list, creating a composite outcome indicating organ damage severe enough to warrant a transplant.

Kidney, heart, liver, and lung transplantations were analysed separately. For eligible participants that received anthracycline chemotherapy as part of their treatment for cancer, the total anthracycline dose (doxorubicin equivalent dose) was calculated with doxorubicin doses equivalent to daunorubicin doses and idarubicin doses multiplied by three. For each CCSS participant who received radiotherapy, doses were reconstructed with age-specific computational phantoms, scaled any age from newborn to adult (age 19 years old). Using previously described methods for kidney, heart, and lungs, mean organ doses were estimated by averaging all the calculation points in the organ with blocking taken in to account using standarised blocking by field. The maximum target dose to the liver was estimated from the total prescribed dose from all overlapping fields in the abdomen rather than mean organ dose because details about liver blocking were incomplete.[6,19]

## Statistical analysis

Demographic and cancer treatment factors relevant to each organ transplant type were summarised descriptively. We calculated the cumulative incidence of the proportion of survivors who received transplants and had organ damage severe enough to be considered for solid organ transplantation by being placed on the waiting list over time after study entry, treating death as a competing risk and censoring on Dec 31, 2013. Survivors who had transplant surgery without a waiting list registration event, or for whom no waiting list registration data were available, had their candidate registration date set to the transplant surgery date, making the cumulative incidence of placement on a waiting list a composite endpoint. Among survivors who received a transplant, Kaplan-Meier curves estimated overall survival following first solid organ transplantation using mortality data obtained from the US National Death Index, up to Dec 31, 2013.

Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs for associations between cancer treatments, demographic factors, and risk of becoming a solid organ transplantation candidate or recipient. Sensitivity analyses were done to evaluate how study results might vary if the study included unconfirmed self-reports. Risk factors with a p value of less than 0·10 in univariate analyses were included in multivariable models. Factors not significantly associated with solid organ transplantation were removed from the final model, unless doing so caused a 10% or greater change in the HR estimate for another factor or factors in the model. If an included risk factor was missing, the participant was not included in that analysis. The proportional hazards assumption was verified for each factor included in final models. All p values presented are two-sided. p values less than 0·05 were considered significant and no adjustment was made for multiple comparisons. Statistical analyses were done using SAS version 9.4, and Stata 15.1.

| | CCSS cohort (n=13 318) |
|---|---|
| **Sex** | |
| Female | 6177 (46·4%) |
| Male | 7141 (53·6%) |
| **Race** | |
| Non-Hispanic, white | 11 449/13 223 (86·6%) |
| Non-Hispanic, black | 679/13 223 (5·1%) |
| Hispanic | 743/13 223 (5·6%) |
| Other or mixed race | 352/13 223 (2·7%) |
| Unknown | 95 |
| **Age at primary cancer diagnosis, years** | |
| 0–4 | 5295 (39·8%) |
| 5–9 | 2922 (21·9%) |
| 10–14 | 2687 (20·2%) |
| 15–20 | 2414 (18·1%) |
| **Age at last follow-up*, years** | |
| <20 | 612/13 311 (4·6%) |
| 20–29 | 989/13 311 (7·4%) |
| 30–39 | 5147/13 311 (38·7%) |
| 40–49 | 4805/13 311 (36·1%) |
| ≥50 | 1758/13 311 (13·2%) |
| Unknown† | 7 |
| **Primary cancer diagnosis** | |
| Leukaemia | 4502 (33·8%) |
| CNS tumour | 1639 (12·3%) |
| Hodgkin lymphoma | 1846 (13·9%) |
| Non-Hodgkin lymphoma | 1022 (7·7%) |
| Kidney (Wilms') tumour | 1162 (8·7%) |
| Neuroblastoma | 866 (6·5%) |
| Soft tissue sarcoma | 1167 (8·8%) |
| Bone tumour | 1114 (8·4%) |
| **Chemotherapy exposure** | |
| Dactinomycin | 2300/11591 (19·8%) |
| Anthracycline | 4574/11548 (39·6%) |
| Carmustine | 460/11598(4·0%) |
| Bleomycin | 658/11581 (5·7%) |
| Busulfan | 22/11601 (0·2%) |
| Lomustine | 395/11595 (3·4%) |
| Cisplatin | 604/11599 (5·2%) |
| Cyclophosphamide | 5132/11554 (44·4%) |
| Ifosfamide | 62/11602 (0·5%) |
| Melphalan | 116/11603 (1·0%) |
| Methotrexate (intravenous or intramuscular) | 2501/11574 (21·6%) |
| 6-mercaptopurine | 3657/11604 (31·5%) |
| 6-thioguanine | 1073/11604 (9·2%) |
| **Radiation dose** | |
| Kidney, mean dose, Gy | |
| None | 3849/11 303 (34·1%) |
| >0 to 10 | 6832/11 303 (60·4%) |
| >10 to 20 | 546/11 303 (4·8%) |
| >20 | 76/11 303 (0·7%) |
| Unknown | 2015 |
| Heart, mean dose, Gy | |
| None | 3853/11 320 (34·0%) |
| >0 to 10 | 4847/11 320 (42·8%) |
| >10 to 20 | 939/11 320 (8·3%) |
| >20 to 30 | 627/11 320 (5·5%) |
| >30 | 1054/11 320 (9·3%) |
| Unknown | 1998 |
| Liver, maximum tumour dose, Gy | |
| None | 3848/11 372 (33·8%) |
| >0 to 20 | 5531/11 372 (48·6% |
| >20 | 1993/11 372 (17·5%) |
| Unknown | 1946 |
| Lung, mean dose, Gy | |
| None | 3850/11 314 (34·0%) |
| >0 to 10 | 5761/11 314 (50·9%) |
| >10 | 1703/11 314 (15·1%) |
| Unknown | 2004 |
| **Total body irradiation** | |
| No | 11 196/11 381 (98·4%) |
| Yes | 185/11 381 (1·6%) |
| Unknown | 1937 |

(Table 1 continues in next column)

(Continued from previous column)

Data are n (%) or n/N (%). Denominators for all percentage calculations are the number of participants for whom information was available. Approximately 2000 (15%) survivors did not have available treatment information (exact numbers are different for each chemotherapy agent and are shown in the table), primarily because they or their proxy did not sign a medical release, or because of missing information about chemotherapy exposures or routes of delivery, or data needed to calculate radiotherapy dosimetry to a specific organ. CCSS=Childhood Cancer Survivor Study. *End of follow-up was Dec 31, 2013, or the death date for participants who died before the end of 2013. †Seven participants are omitted because of missing death date.

***Table 1:*** **Baseline and treatment characteristics**


## Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.


## Results

Characteristics of the 13 318 included CCSS participants enrolled between Jan 1, 1970, and Dec 31, 1986, are summarised (table 1). Participants were more likely to be male, white non-Hispanic, with median age at diagnosis of 6 years (IQR 3–13) and median age at follow-up of 39 years (33–46). Details of therapeutic exposures are also summarised (table 1). 103 solid organ transplants for 100 survivors were identified after linkage (table 2), 54 of whom had data indicating waiting list of translantation recorded in CCSS and OPTN, and 46 of whom had this data recorded in OPTN only (of whom 33 only had this data recorded after last contact with CCSS). Three survivors had solid organ transplantation that

| | Organ transplantations* (n=103) | Waiting list registrations† (never received an organ) (n=67) | Total number of transplantations and waiting list registrations (n=170) |
|---|---|---|---|
| Kidney | 50 (49%) | 21 (31%) | 71 (42%) |
| Heart | 37 (36%) | 25 (37%) | 62 (36%) |
| Liver | 9 (9%) | 15 (22%) | 24 (14%) |
| Lung | 7 (7%) | 6 (9%) | 13 (8%) |

Summary of survivors who were recipients of or placed on a waiting list for a solid organ transplantation more than 5 years after diagnosis of childhood cancer. *Three survivors with a kidney transplant previously underwent a different solid organ transplant. †Some survivors placed on the waiting list who did not receive a transplant were listed for more than one organ.

*Table 2:* **Solid organ transplantations and waiting list registrations**

had occurred before OPTN inception; for all three, transplantation was determined by self-report on a questionnaire (with some information in OPTN for one survivor). Four participants reported solid organ transplantation (two kidney, one heart, one liver) after 1988 but could not be linked to an OPTN record and were excluded from the analyses. Three survivors with a kidney transplant previously underwent transplantation with a different solid organ. An additional 67 participants were placed on the waiting list without receiving a transplanted organ, with some survivors being listed for more than one organ. The most common solid organ transplantation was kidney, followed by heart, liver, and lung. Age at original cancer diagnosis, age at solid organ transplantation, cancer diagnosis preceding the transplantation, and treatment exposures based on transplantation organ group are summarised (table 3). We have also presented results of the univariate analyses (appendix pp 4–5) for variables that were included in the multivariable analyses (table 4). For each organ transplant risk factor analysis outlined, sensitivity analyses that included unsubstantiated reports of organ transplants as events were done and showed no change in observed associations (data not shown).

71 survivors had end-stage kidney disease warranting kidney transplantation. Of those, 21 were placed on a waiting list without receiving a kidney, whereas 50 survivors received a kidney transplant (table 2). At 35 years after cancer diagnosis, cumulative incidence of kidney transplantation was 0·39% (95% CI 0·27–0·51) and cumulative incidence of being placed on the waiting list or receiving a kidney was 0·54% (0·40–0·67; figure 1). Exposure to ifosfamide and receiving total body irradiation were associated with the highest HR for being placed on the waiting list or receiving a kidney transplant. Additional significant factors with increased HRs included unilateral nephrectomy and non-total body irradiation kidney radiation doses of greater than 15 Gy (table 4). The 5-year and 10-year survival estimates from time of kidney transplantation were 93·5% (95% CI 81·0–97·9) and 73·6% (56·0–85·0; figure 2, respectively). Of those patients put on the waiting list who did not receive a kidney, ten (48%) of 21 died before the end of follow-up with a median time from waiting list registration to death of 5·9 years (IQR 0·3–21·8).

62 survivors had end-stage heart failure warranting heart transplantation. Of those, 25 were put on the waiting list without receiving a heart, whereas 37 survivors received a heart transplant (table 2). At 35 years after cancer diagnosis, cumulative incidence of heart transplantation was 0·30% (95% CI 0·20–0·40) and cumulative incidence of being placed on the waiting list or receiving a heart was 0·49% (0·36–0·62%; figure 1). The HR generally increased in a dose-dependent manner with anthracycline exposure and heart radiation dose (table 4). The 5-year survival estimate from time of heart transplantation was 80·6% (95% CI 63·6–90·3; figure 2). Of those placed on the waiting list who did not receive a heart, 20 (80%) of 25 died before the end of follow-up with a median time from waiting list registration to death of 0·7 years (IQR 0·1–4·5).

24 survivors had end-stage liver disease warranting liver transplantation. Of those, 15 were placed on the waiting list but did not receive a liver, and nine had a liver transplant (table 2). At 35 years after cancer diagnosis, cumulative incidence of liver transplantation was 0·07% (95% CI 0·02–0·12) and cumulative incidence of being placed on the waiting list or receiving a liver was 0·19% (0·10–0·27; figure 1). Significant associations were identified for dactinomycin and methotrexate (table 4). The 5-year survival estimate from time of liver transplantation was 27·8% (95% CI 4·4–59·1; figure 2). Of those registered on the waiting list who did not receive a liver, 11 (73%) of 15 died before the end of follow-up, with a median time from registration on the waiting list to death of 0·9 years (IQR 0·2–4·0).

13 survivors had pulmonary damage severe enough to warrant lung transplantation. Of those, six were placed on the waiting list but did not receive a lung, and seven received a lung transplant (table 2). At 35 years after cancer diagnosis, cumulative incidence of lung transplantation was 0·05% (95% CI 0·01–0·08) and cumulative incidence of being placed on the waiting list or receiving a lung was 0·10% (0·04–0·16; figure 1). Exposure to carmustine and lung radiation over 10 Gy were significantly associated with lung transplantation or being placed on a lung transplantation waiting list (table 4). The 5-year survival estimate from time of lung transplantation was 34·3% (95% CI 4·8–68·6; figure 2). Of those placed on the waiting list but not receiving a lung, five (83%) of six died before the end of follow-up with a median time from waiting list registration to death of 0·7 years (IQR 0·3–3·1).

## Discussion

To our knowledge, this is the first study to link a population of survivors of common childhood cancers with the OPTN that provides outcomes from the largest series of cancer survivors with solid organ transplantation, to date. Incidence of kidney, heart, liver, or lung

| | Survivors needing solid organ transplantation |
|---|---|
| **Kidney transplantation (n=71)** | |
| Demographic characteristics | |
| Age at cancer diagnosis, years | 2 (<1–9) |
| Age at transplantation, years | 25 (20–35) |
| Time from cancer diagnosis to transplantation, years | 21 (17–29) |
| Time after waiting list registration or transplantation until end of follow-up for participants alive, years | 9 (5–14) |
| Time between waiting list registration or transplantation and death of participants, years | 7 (1–10) |
| Diagnosis | |
| Kidney tumour | 33 (46%) |
| Acute lymphoblastic leukaemia | 9 (13%) |
| Acute myeloid and other leukaemia | 4 (6%) |
| Non-Hodgkin lymphoma | 8 (11%) |
| Neuroblastoma | 7 (10%) |
| Bone cancer | 7 (10%) |
| Soft tissue sarcoma | 2 (3%) |
| CNS tumour | 1 (1%) |
| Cancer treatment | |
| Cisplatin (n=63) | |
| No | 59 (94%) |
| Yes | 4 (6%) |
| Ifosfamide (n=63) | |
| No | 59 (94%) |
| Yes | 4 (6%) |
| Methotrexate (intravenous or intramuscular) (n=63) | |
| No | 55 (87%) |
| Yes | 8 (13%) |
| Nephrectomy (n=63) | |
| No | 39 (62%) |
| Yes (all unilateral) | 24 (38%) |
| Mean kidney radiation dose,*† Gy (n=63) | |
| None | 26 (41%) |
| >0 to 10 | 18 (29%) |
| >10 to 15 | 8 (13%) |
| >15 to 20 | 9 (14%) |
| >20 | 2 (3%) |
| Total body irradiation (n=63) | |
| No | 59 (94%) |
| Yes | 4 (6%) |
| **Heart transplantation (n=62)** | |
| Demographic characteristics | |
| Age at cancer diagnosis, years | 6 (3–11) |
| Age at transplantation, years | 28 (21–32) |
| Time from cancer diagnosis to transplantation, years | 17 (13–26) |
| Time after waiting list registration or transplantation until end of follow-up for participants alive, years | 11 (6–20) |
| Time between waiting list registration or transplantation and death of participants, years | 1 (0–5) |

(Table 3 continues in next column)

| | Survivors needing solid organ transplantation |
|---|---|
| (Continued from previous column) | |
| Diagnosis | |
| Bone cancer | 15 (24%) |
| Acute lymphoblastic leukaemia | 8 (13%) |
| Acute myeloid and other leukaemia | 6 (10%) |
| Hodgkin lymphoma | 12 (19%) |
| Non-Hodgkin lymphoma | 10 (16%) |
| Kidney tumour | 7 (11%) |
| Soft tissue sarcoma | 3 (5%) |
| Neuroblastoma | 1 (2%) |
| Cancer treatment | |
| Anthracyclines, mg/m$^2$ (n=53) | |
| None | 9 (17%) |
| >0 to 150 | 3 (6%) |
| >150 to 300 | 4 (8%) |
| >300 to 450 | 16 (30%) |
| >450 | 21 (40%) |
| Cisplatin (n=56) | |
| No | 53 (95%) |
| Yes | 3 (5%) |
| Cyclophosphamide, mg/m$^2$ (n=54) | |
| None | 27 (50%) |
| >0 to 10 000 | 10 (19%) |
| >10 000 to 20 000 | 12 (22%) |
| >20 000 | 5 (9%) |
| Mean heart radiation dose*,Gy (n=53) | |
| None | 10 (19%) |
| >0 to 10 | 25 (47%) |
| >10 to 20 | 3 (6%) |
| >20 to 30 | 4 (8%) |
| >30 | 11 (21%) |
| Total body irradiation (n=53) | |
| No | 52 (98%) |
| Yes | 1 (2%) |
| **Liver transplantation (n=24)** | |
| Demographic characteristics | |
| Age at cancer diagnosis, years | 6 (4–9) |
| Age at transplantation, years | 37 (25–38) |
| Time from cancer diagnosis to transplantation, years | 27 (20–29) |
| Time after waiting list registration or transplantation until end of follow-up for participants alive, years | 6 (1–20) |
| Time between waiting list registration or transplantation and death of participants, years | 1 (0–3) |
| Diagnosis | |
| Acute lymphoblastic leukaemia | 8 (33%) |
| Acute myeloid and other leukaemia | 3 (13%) |
| Bone cancer | 4 (17%) |
| Soft tissue sarcoma | 4 (17%) |
| Kidney tumour | 3 (13%) |

(Table 3 continues in next column)

| | Survivors needing solid organ transplantation |
|---|---|
| (Continued from previous column) | |
| Non-Hodgkin lymphoma | 1 (4%) |
| Neuroblastoma | 1 (4%) |
| Cancer treatment | |
| Dactinomycin (n=21) | |
| No | 12 (57%) |
| Yes | 9 (43%) |
| Busulfan (n=21) | |
| No | 21 (100%) |
| Yes | 0 |
| Cyclophosphamide, mg/m$^2$ (n=20) | |
| None | 5 (25%) |
| >0 to 10 000 | 12 (60%) |
| >10 000 to 20 000 | 2 (10%) |
| >20 000 | 1 (5%) |
| Melphalan (n=21) | |
| No | 21 (100%) |
| Yes | 0 |
| Methotrexate (intravenous or intramuscular) (n=21) | |
| No | 11 (52%) |
| Yes | 10 (48%) |
| Maximum abdomen tumour radiation dose*, Gy (n=19) | |
| None | 8 (42%) |
| >0 to 20 | 6 (32%) |
| > 20 | 5 (26%) |
| Total body irradiation (n=19) | |
| No | 18 (95%) |
| Yes | 1 (5%) |
| **Lung transplantation (n=13)** | |
| Demographic characteristics | |
| Age at cancer diagnosis, years | 12 (<1–16) |
| Age at transplantation, years | 30 (27–37) |
| Time from cancer diagnosis to transplantation, years | 21 (14–29) |
| Time after waiting list registration or transplantation until end of follow-up for participants alive, years | 5 (1–15) |
| Time between waiting list registration or transplantation and death of participants, years | 3 (1–4) |
| Diagnosis | |
| Acute lymphoblastic leukaemia | 3 (23%) |
| Acute myeloid and other leukaemia | 2 (15%) |
| Hodgkin lymphoma | 3 (23%) |
| Kidney tumour | 2 (15%) |
| Non-Hodgkin lymphoma | 1 (8%) |
| Neuroblastoma | 1 (8%) |
| CNS tumour | 1 (8%) |
| Cancer treatment | |
| Carmustine (n=11) | |
| No | 8 (73%) |
| Yes | 3 (27%) |
| Bleomycin (n=11) | |
| No | 10 (91%) |
| Yes | 1 (9%) |
| Busulfan (n=11) | |
| No | 11 (100%) |
| Yes | 0 |
| Lomustine (n=11) | |
| No | 11 (100%) |
| Yes | 0 |
| Cisplatin (n=11) | |
| No | 10 (91%) |
| Yes | 1 (9%) |
| Cyclophosphamide, mg/m$^2$ (n=9) | |
| None | 4 (44%) |
| >0 to 10 000 | 4 (44%) |
| >10 000 to 20 000 | 1 (11%) |
| >20 000 | 0 |
| Methotrexate (intravenous or intramuscular) (n=11) | |
| No | 7 (64%) |
| Yes | 4 (36%) |
| Mean lung radiation dose*†, Gy (n=11) | |
| None | 2 (18%) |
| >0 to 10 | 4 (36%) |
| >10 | 5 (46%) |
| Total body irradiation (n=11) | |
| No | 9 (82%) |
| Yes | 2 (18%) |

Data are median (IQR) or n (%). Treatment data availability for kidney transplantation: complete (n=61), partial (n=4), none (n=6). Treatment data availability for heart transplantation: complete (n=52), partial (n=5), none (n=5). Treatment data availability for liver transplantation: complete (n=19), partial (n=2), none (n=3). Treatment data availability for lung transplantation: complete (n=11), partial (n=0), none (n=2). CCSS=Childhood Cancer Survivor Study. *Radiation received, as total body irradiation is included in the organ-specific dose calculations. †If the right and left kidneys or lungs received different amounts of radiation, the survivor was classified on the basis of the kidney (or lung) with the lesser degree of radiation exposure.

***Table 3*: Cancer treatment exposures for participants in the CCSS survivor cohort who received or registered on the waiting list for an organ transplantation**

transplantation is low among survivors of childhood cancer at a median age of 39 years. There are clear organ-specific radiation and chemotherapy exposures that increase risk of requiring solid organ transplantation following cure of childhood cancer. Direct comparison of 5-year survival after transplantation with those recipients that were not childhood cancer survivors was not done because a relevant dataset with covariates was not available. However, publicly available OPTN data[20] as of April 26, 2019 show that for kidney and heart transplants, the 5-year survival and 95% CIs for people aged 18–34 years who received transplants between 2008 and 2015 for any diagnosis (kidney 95·5% [95% CI

| | HR (95% CI) | p value |
|---|---|---|
| **Kidney waiting list registration or transplantation** | | |
| Ifosfamide | | |
| No | 1 (ref) | .. |
| Yes | 24·9 (7·4–83·5) | <0·0001 |
| Methotrexate (intravenous or intramuscular) | | |
| No | 1 (ref) | .. |
| Yes | 0·6 (0·3–1·5) | 0·30 |
| Mean kidney radiation dose, Gy | | |
| None | 1 (ref) | .. |
| >0 to 10* | 0·4 (0·2–0·7) | 0·0040 |
| >10 to 15* | 1·6 (0·6–4·0) | 0·35 |
| >15 to 20* | 3·6 (1·5–8·5) | 0·0041 |
| >20* | 4·6 (1·1–19·6) | 0·040 |
| Total body irradiation | 6·9 (2·3–21·1) | 0·0007 |
| Nephrectomy | | |
| No | 1 (ref) | .. |
| Yes (all unilateral) | 4·2 (2·3–7·7) | <0·0001 |
| Age at primary cancer diagnosis, years | | |
| 0–4 | 1·5 (0·6–3·7) | 0·38 |
| 5–9 | 1·2 (0·4–3·3) | 0·72 |
| 10–14 | 0·8 (0·2–2·6) | 0·71 |
| 15–20 | 1 (ref) | .. |
| **Heart waiting list registration or transplantation** | | |
| Cyclophosphamide, mg/m² | | |
| None | 1 (ref) | .. |
| >0 to 10 000 | 0·3 (0·1–0·6) | 0·0018 |
| >10 000 to 20 000 | 0·8 (0·4–1·7) | 0·57 |
| >20 000 | 1·3 (0·5–3·7) | 0·61 |
| Anthracyclines, mg/m² | | |
| None | 1 (ref) | .. |
| >0 to 150 | 8·4 (2·2–32·6) | 0·0020 |
| >150 to 300 | 5·0 (1·3–19·5) | 0·021 |
| >300 to 450 | 26·5 (9·9–71·0) | <0·0001 |
| >450 | 94·2 (35·3–251·2) | <0·0001 |
| Mean heart radiation dose, Gy | | |
| None | 1 (ref) | .. |
| >0 to 10 | 2·2 (1·0–4·8) | 0·050 |
| >10 to 20 | 1·9 (0·5–7·3) | 0·33 |
| >20 to 30 | 6·1 (1·8–20·6) | 0·0035 |
| >30 | 19·7 (7·1–54·2) | <0·0001 |
| **Liver waiting list registration or transplantation** | | |
| Dactinomycin | | |
| No | 1 (ref) | .. |
| Yes | 3·8 (1·3–11·3) | 0·016 |
| Cyclophosphamide | | |
| No | 1 (ref) | .. |
| Yes | 2·4 (0·8–7·5) | 0·13 |
| Methotrexate (intravenous or intramuscular) | | |
| No | 1 (ref) | .. |
| Yes | 3·3 (1·0–10·2) | 0·041 |
| Antimetabolites (6-MP or 6-TG) | | |
| No | 1 (ref) | .. |
| Yes | 1·6 (0·5–5·1) | 0·46 |
| Maximum abdomen tumor radiation dose, Gy | | |
| None | 1 (ref) | .. |
| >0 to 20* | 0·4 (0·1–1·5) | 0·18 |
| >20* | 2·2 (0·6–7·8) | 0·21 |
| Total body irradiation | 2·2 (0·3–18·6) | 0·48 |
| Sex | | |
| Male | 1 (ref) | .. |
| Female | 0·4 (0·2–1·2) | 0·11 |
| **Lung waiting list registration or transplantation** | | |
| Carmustine | | |
| No | 1 (ref) | .. |
| Yes | 12·3 (3·1–48·9) | 0·0004 |
| Methotrexate (intravenous or intramuscular) | | |
| No | 1 (ref) | |
| Yes | 2·7 (0·8–9·9) | 0·12 |
| Mean lung radiation dose, Gy | | |
| None | 1 (ref) | .. |
| >0 to 10 | 1·5 (0·3–8·3) | 0·63 |
| >10 | 15·6 (2·6–92·7) | 0·0025 |
| Age at primary cancer diagnosis, years | | |
| 0–4 | 9·7 (1·0–93·9) | 0·050 |
| 5–9 | 1·9 (0·1–31·3) | 0·65 |
| 10–14 | 4·2 (0·4–40·5) | 0·22 |
| 15–20 | 1 (ref) | .. |
| Sex | | |
| Male | 1 (ref) | .. |
| Female | 3·3 (0·9–12·4) | 0·083 |

Only cancer treatment exposures associated with significant increases in risk for solid organ transplantation are displayed. Other factors examined include: sex, age at primary cancer diagnosis, cisplatin, cyclophosphamide and busulfan (multiple models); antimetabolites, melphalan and abdominal radiation (liver model); bleomycin and lomustine (lung model). CCSS=Childhood Cancer Survivor Study. HR=hazard ratio. 6-MP=6-mercaptopurine. 6-TG=6-thioguanine. *Non-total body irradiation.

***Table 4:*** **Risk factors associated with organ-specific waiting list registration or transplantation in the CCSS survivor cohort**

95·0–95·9] and heart 74·9% [71·8–77·7]) were similar to those among childhood cancer survivors (93·5% [81·0–97·9] and 80·6% [63·6–90·3], respectively). For liver and lung transplants, the 5-year survival was higher in the general population (liver 79·5% [95% CI 77·2–81·6] and lung 54·9% [51·2–58·5]) than in childhood cancer survivors (27·8% [4·4–59·1] and 34·3% [4·8–68·6], respectively). In the CCSS cohort, fewer than ten childhood cancer survivors received a liver or lung transplant, which limits the ability to draw meaningful conclusions relative to the general population. Survival following kidney, heart, liver, or lung transplantation shows that solid organ transplantation should be considered for 5-year survivors with severe

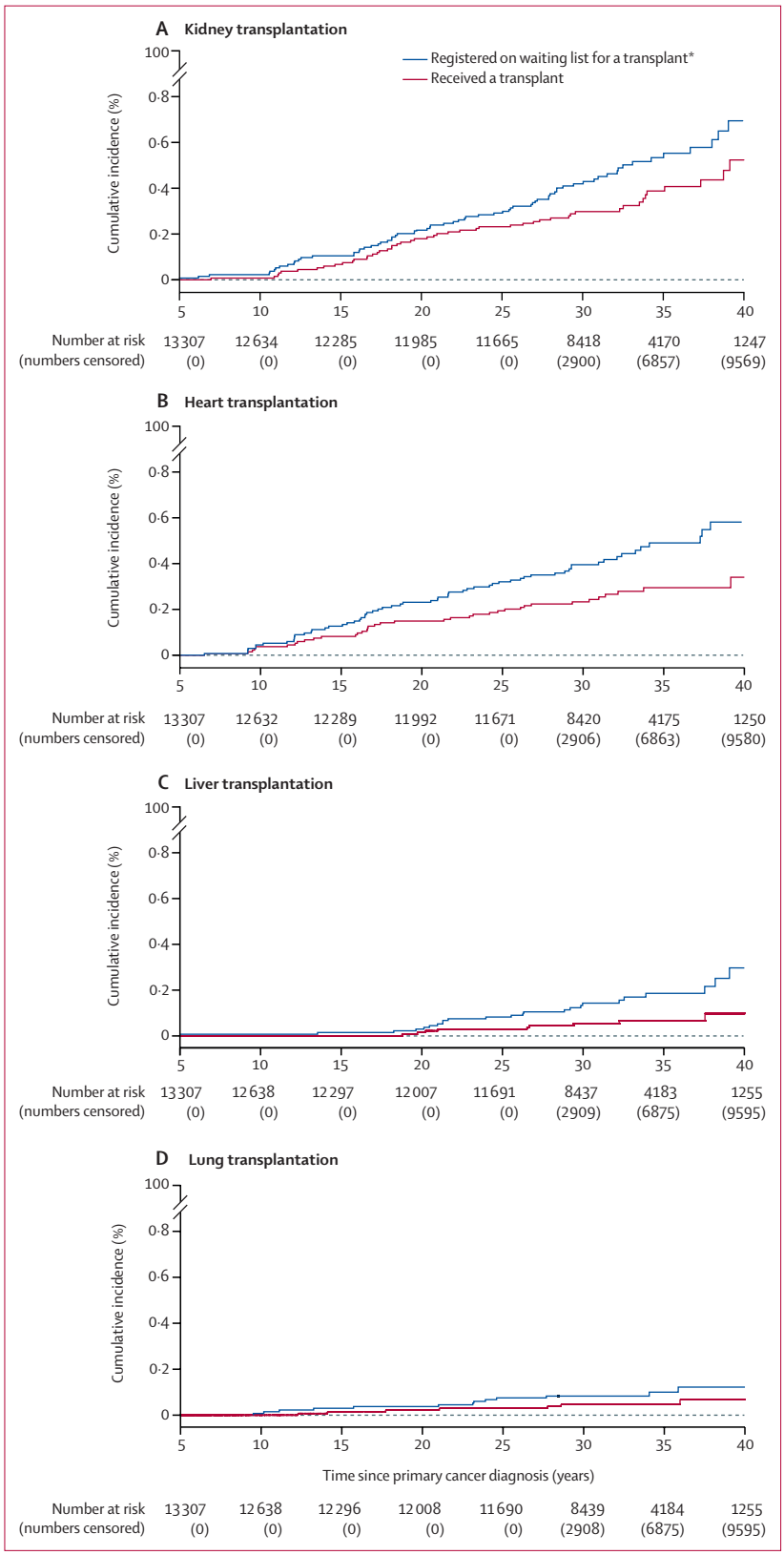


***Figure 1:*** **Cumulative incidence of transplantation and registration on transplant waiting list among CCSS survivors**
CCSS=Childhood Cancer Survivor Study. *Includes patients who received a living donor transplant without a preceding waiting list registration.

end-organ failure, particularly for those with renal and cardiac failure.

Established general guidelines exist regarding the evaluation of solid organ transplant candidates.[21–23] However, guidelines regarding cancer involve excluding patients with untreated or untreatable malignancy and often mention the need for oncology clearance before a patient is considered eligible. Ambiguity can result in different practice among treating institutions, owing in part to the scarce evidence available in these populations. Solid organ transplantation could be a part of first-line therapy, such as for hepatoblastoma, for which outcomes look promising (US Scientific Registry of Transplant Recipients and University of Pittsburgh registry)[24] or could be done when organ failure is a consequence of acute toxicity. The CCSS cannot assess all organ transplantations following cancer diagnosis, since cohort entry is 5 years after diagnosis. These findings inform oncologists and organ transplant physicians about survivors who are at least 5 years along from original diagnosis regarding risk factors and outcomes.

Although kidney transplantation is reported in survivors of childhood cancer,[10–12] cumulative incidence and survival after kidney transplantation is understudied. Risk factors for renal toxicity, in general, are well established and include total body irradiation,[25] nephrectomy,[12] radiotherapy, platinum agents, and ifosfamide.[25,26] This study further details of the associations of ifosfamide, modest radiation exposure of the kidneys, and unilateral nephrectomy with end-organ failure severe enough to require solid organ transplantation. With radiotherapy, we identified increased risk at exposures of greater than 15 Gy. No risk was associated with platinum agents, although with increasing age and follow-up, that risk might emerge. Notably, survival of childhood cancer survivors who receive kidney transplants steadily decreases even after 5-years following transplantation, which is similar to observations in overall analyses of kidney transplantation with respect to graft and overall survival.[27,28]

More reports on heart transplantation exist in the literature for childhood cancer survivors than for any other solid organ transplantation, and this procedure is often associated with good long-term survival.[10,13–15] Although not as common as kidney transplantation in our cohort, it was the second most common organ transplanted. Here we establish excellent 5-year survival, similar to the only other adequately sized previous study, which showed 74% survival at 5 years and 67% at 10 years after the procedure.[13] Known risk factors for heart failure were also identified as risk factors for heart

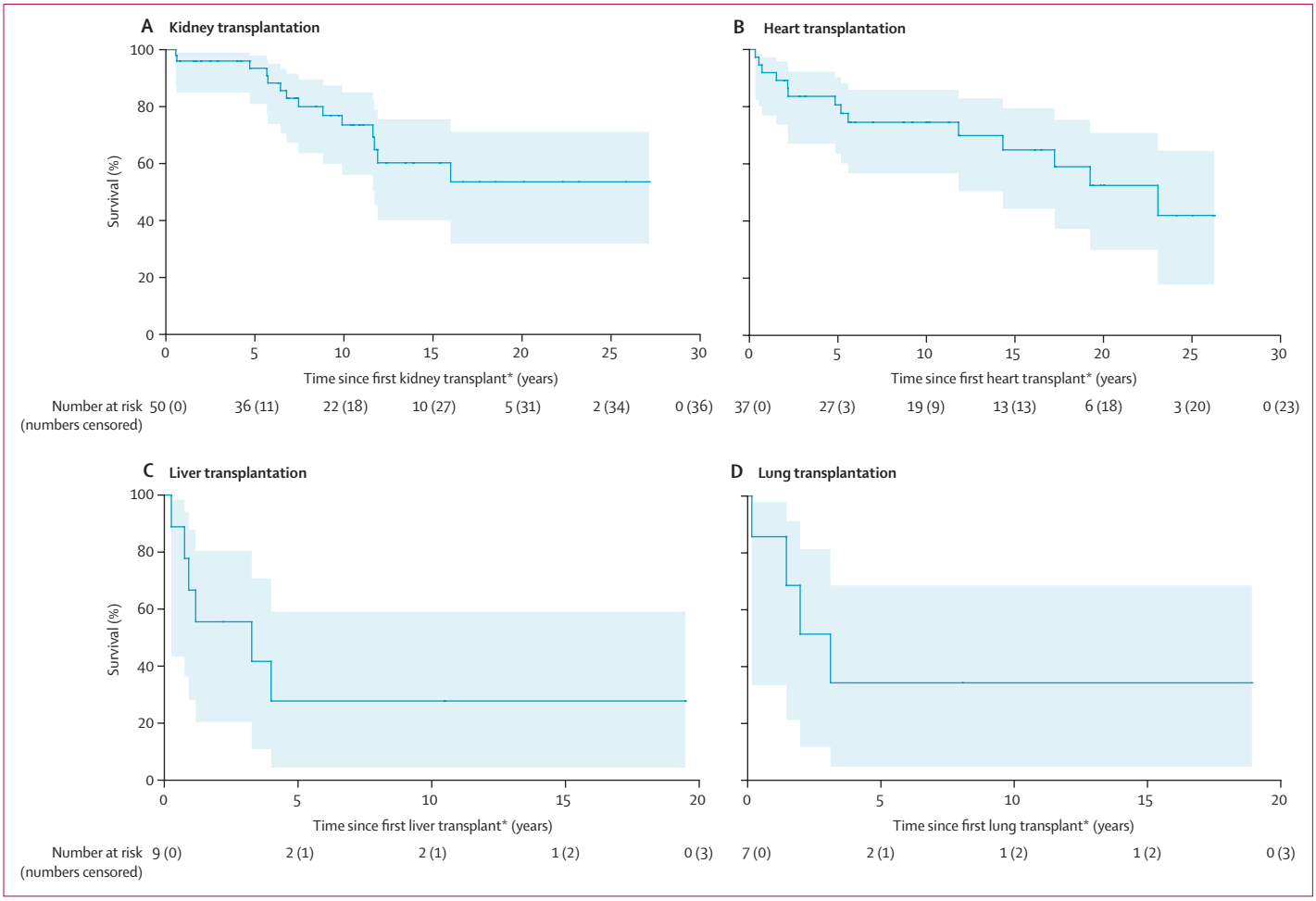


***Figure 2:*** **Kaplan-Meier plots showing overall survival of CCSS survivors following solid organ transplantation**
Shaded area is the 95% CI. CCSS=Childhood Cancer Survivor Study. *Analysis is restricted to cancer survivors who received their first organ transplant after CCSS cohort entry.

transplantation, including anthracyclines and cardiac radiotherapy, each in a dose-dependent manner. A better understanding of these risks as independent or potentiating, within each dose level, would be ideal; however, not enough events occurred in separate strata to examine this association. No other exposures were found to be associated with need for heart transplantation in this study.

Liver transplantation can play a role in the initial treatment of paediatric cancer, particiularly in advanced stage hepatoblastoma.[24] The CCSS did not include patients with hepatoblastoma and did not include any liver transplants that occurred less than 5 years from diagnosis. Liver transplant used to treat late hepatotoxicty in survivors of childhood cancer is less frequently reported than transplants done for initial therapy.[10] For these reasons, a very low number of liver transplants compared with other organ transplants are reported in this study. Even though this cohort describes the largest series of liver transplants to date, the small number of survivors with a liver transplant for late complications results in difficulty interpreting survival estimates and risk factor analyses. Importantly, we observed that long-term survival is possible after liver transplantation in survivors of childhood cancer. The most significant risk factors for hepatotoxicity include radiation therapy, haematopoietic stem cell transplantation, and infectious hepatitis.[4,29] Although methotrexate and dactinomycin are known to cause acute hepatotoxicity, this study shows the risk that these two agents carry for long-term hepatotoxicity, not recognised to date. Abdominal radiation was not identified as a risk factor, possibly because of low incidence of solid liver transplantation. Further assessments should be done as this population ages.

Lung transplantation was the least common procedure. Previously reported in case reports or case series,[10,13] very little is known regarding this therapeutic intervention in childhood cancer survivors. Although the current analysis is the largest reported, low incidence makes interpretation of survival and risk factor analyses difficult. Despite this, we showed that long-term survival is possible after lung transplantation in cancer survivors.

Risk factors for the most serious lung toxicity include carmustine and lung radiation.[6] These two exposures are additionally associated with lung damage severe enough to require lung transplantation.

A concern for any survivor considering solid organ transplantation is the required use of prolonged immunosuppression, and whether that could lead to relapse of primary cancer or development of secondary malignancies. Original reports regarding these issues might have restricted survivors' access to organ transplants.[30] Although secondary malignancies can be a substantial issue in childhood cancer survivors as well as survivors of solid organ transplantations, the majority of these secondary malignancies are skin cancers,[31] for which good screening is available. The current study was not able to assess risks of relapse or secondary malignancies because many survivors had their transplantations after the last recorded CCSS contact. Only very small amounts of data are available regarding the risk of relapse or secondary malignancies and additional research is needed. Study of this rare outcome in a later, more recently treated CCSS expansion cohort of paediatric cancer survivors (diagnosed from 1987–1999), would be valuable in determining if changes in treatment exposure would reduce the risk for solid organ transplantation.

Limitations of this study include the fact that relatively small numbers of survivors receive solid organ transplantations, especially liver and lung transplantations. CCSS is often limited by self-reported outcomes, but linkage to OPTN with direct assessment of solid organ transplantations overcomes that limitation. This study is also limited to the US population, and it is unknown if results can be generalised or will be different in other populations. The exclusion of children diagnosed with hepatoblastoma, retinoblastoma, and germ cell tumours from the CCSS cohort might have affected the total number of 5-year survivors who received transplantations. The use of solid organ transplantations in cancer therapy or for acute complications of treatment is open for further study outside the context of CCSS. The strengths of this study include the linkage of two large databases, each with a wealth of information, to define this large cohort and create the first assessments of cumulative incidence, survival, and risk factor analyses for this unique survivor population.

This study provides evidence for health-care providers regarding risk of life-threatening solid organ failure and transplantation occurring 5 years or longer after diagnosis of common paediatric cancers. It provides evidence for efficacy of solid organ transplantation in recipients who have a history of paediatric cancer, informs practice in organ transplant subspecialties, and provides data for third-party payers, who might resist paying for these rare life-saving procedures after a cancer diagnosis, on the basis of a small number of case reports.

**Contributors**
ACD and AMT designed the study. GTA and LLR provided financial support. All authors were involved in acquisition of the data. KS and WML were involved in analysis of the data. All authors were involved in interpretation of the data. ACD drafted the manuscript. All authors were involved in revising the work for important intellectual content. All authors have approved the final version of the work for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Declaration of interests**
Following completion of this study, ACD became employed by bluebird bio, which provided no support and had no oversight over or input into the completion of this study. All other authors declare no competing interests.

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