

1. TITLE: Solid organ transplant in 5 year survivors of pediatric cancer.

2.WORKING GROUP /INVESTIGATORS: Chronic Diseases Working Group

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3.BACKGROUND AND RATIONALE

Morbidity and mortality from cardiac, pulmonary and other medical conditions occur in pediatric cancer survivors as early as five years from diagnosis.¹⁻⁶ Some life-threatening late complications of treatment for childhood cancer are treated with solid organ transplantation.^{3,7,8} Review of the literature shows a limited number of reports of cancer survivors undergoing cardiac, renal, liver, and pulmonary transplantation.⁷⁻⁹⁻¹⁷

Long-term outcomes of childhood cancer survivors after a solid organ transplant are largely unknown. A study based on the National Registry of Childhood Tumors and

the United Kingdom Transplant database identified 46 pediatric cancer survivors who were recipients of cardiac or cardiac/pulmonary transplant. Of those patients the five-year and ten-year actuarial survival were 74% and 67%, respectively. Transplant complications accounted for all mortality, although two of 36 assessable patients developed relapses following cardiac transplant.¹¹ Beitinjaneh reviewed solid organ transplant following hematopoietic stem cell transplant in the literature, adding 12 cases. Of the five pediatric patients undergoing solid organ transplant following hematopoietic stem cell transplant, two received kidney allografts, two received liver transplant, and one a lung transplant. One patient receiving a liver transplant and one receiving a renal allograft were long term survivors. One patient was lost to follow up and the two remaining patients died, one from a fungal infection and one from multi-system organ failure one month following her lobar lung transplant.⁷ There are a few other case reports of cardiac transplant in children following treatment for pediatric cancers.^{12,15}

Prolonged immunosuppression is necessary for solid organ transplantation. Concerns regarding relapse and the development of secondary malignancies, generated from the renal allograft literature in the 1970s, may limit survivors' access to organ transplant.^{18,19} Relapse is also a concern for other organ transplant recipients. Ten percent of patients (mostly adult) transplanted with a solid organ after the diagnoses of Hodgkin lymphoma or non-Hodgkin lymphoma relapse. The likelihood of relapse increased in patients treated with Hodgkin lymphoma who were splenectomized.²⁰ More recent and promising findings demonstrate long-term survival, particularly following cardiac transplantation^{7,11,13-16,20} With survival from pediatric cancer improving and the availability of well-accepted guidelines for surveillance of survivors for end-organ damage, the frequency of solid organ transplantation among survivors is increasing, as demonstrated in the United Kingdom.¹¹ The CCSS cohort is large enough to provide data for a descriptive analysis of these rare transplants.

4.SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES

1. Primary aim: This is a descriptive study of outcomes following solid organ transplant (SOT) in five-year survivors of pediatric cancer diagnosed from 1970 to 1986 focusing on subsequent mortality, recurrence, and second malignant neoplasms.
2. Objectives:
 - a. The primary objective is to describe the mortality, development of second malignancies, and recurrence of primary tumor in cohort members reporting a solid organ transplant between five years post cancer diagnosis and Follow-Up 2007. Descriptive information on a matched group of cancer survivors who did not receive a solid organ transplant will also be summarized.
 - b. Secondary objectives are:
 - i. To report the frequency of SOT in the CCSS cohort.

- ii. To report the time from cancer diagnosis to SOT in five year survivors of childhood cancer.
- iii. To describe age at diagnosis, gender, cancer diagnosis, treatment exposure (irradiation to specific sites, specific chemotherapy agents, nephrectomy) in childhood cancer survivors undergoing heart, lung, kidney or liver transplantation more than five years from diagnosis. Descriptive information on treatment exposures for a matched group of subjects that did not undergo solid organ transplantation will also be summarized.

3. Hypotheses:

This is a descriptive study examining the subsequent incidence of mortality, recurrence of primary cancer, and the development of a second malignant neoplasm in patients following solid organ transplantation relative to similar CCSS cohort subjects who are not recipients of a solid organ transplant.

5. ANALYSIS FRAMEWORK

1. Outcome of interest:

In patients reporting a SOT more than five years from cancer diagnosis on either the Baseline or FU 2007 survey:

- 1. Mortality
 - A. Solid organ transplant and death reported by surrogate at Baseline
 - B. Solid organ transplant reported on Baseline and no response to FU 2007
 - 1. If deceased in the interim (determined via search of the National Death Index), note date and cause of death
 - 2. If not confirmed deceased, censor at the date of NDI search

Censoring notes: Subjects who self-reported a (first) solid organ transplant on FU2007 or who reported SOT at Baseline and also returned the FU2007 questionnaire are known to be alive at FU2007. However, there may be a short interval of additional follow up available via the NDI search. For consistency, we will also review the NDI data for these subjects, noting any late deaths and extending censoring times to the date of the NDI search for survivors.

2. Recurrence after Solid Organ Transplant
 - A. Age at recurrence
 - Data from combination of questionnaires in CCSS database
3. Second malignant neoplasm after Solid Organ Transplant
 - A. Age at SMN (defined as excluding non-melanoma skin cancers) and type of SMN

In the matched study group composed of survivors who did not undergo solid organ transplantation, the mortality, recurrence and SMN events will be determined via a similar process.

2. Subject population

1. Inclusion criteria: (please note that patients receiving solid organ transplant prior to five years from diagnosis are NOT eligible for inclusion)

Solid Organ Transplant group: Self-report of Solid Organ Transplant on Baseline or Follow-Up 2007 (at least one survey)

a. Baseline – Yes to any of the following questions *and* >5 years elapsed between cancer diagnosis and SOT

1. I 23 (Heart transplant)
2. I 24 (Lung transplant)
3. I 25 (Kidney transplant)
4. I 27 (Other organ transplant)
 - A. specify type – liver

b. Follow-up 2007 – Yes to any of the following questions *and* >5 years elapsed between cancer diagnosis and SOT

- 1 J 25 (Heart transplant)
- 2 J 26 (Lung transplant)
- 3 J 27 (Kidney transplant)
- 4 J 28 (Liver transplant)

2. Inclusion criteria:

Comparison group (matched)

- a. No report of a heart, lung, kidney or liver transplant on the Baseline or FU2007 questionnaire
- b. Matched for primary cancer diagnosis
- c. Matched for being alive and under observation on CCSS at least as long as the amount of time elapsed from cancer diagnosis to solid organ transplant for the corresponding SOT case
- d. Matched for age at cancer diagnosis within ± 5 years of the SOT recipient's age at cancer diagnosis
- e. Matched for gender

For each SOT case, a fixed number, maximized to the number of matches obtainable for all cases, of comparison group subjects will be randomly selected from among all available survivors meeting the matching criteria for that SOT case.

3. Variables

All SOT recipients and comparison group subjects:

- a. Age at diagnosis (Database)
- b. Age at solid organ transplant (Baseline I 23, I 24, I 25, I 27 – specify liver) and/or FU 2007 J25, J26, J27, J28)
- c. Gender (A2- Baseline)
- d. Cancer diagnosis (Database)
- e. Age at follow-up

Heart transplant recipients and their matched comparison group subjects:

- a. Cumulative anthracycline dose (=doxorubicin + daunorubicin + 3*idarubicin)
- b. Cumulative cyclophosphamide dose
- c. Cumulative cis-platinum dose
- d. Heart radiation (dose)
- e. Anthracycline plus heart irradiation: (Y/N)
- f. Cyclophosphamide plus heart irradiation: (Y/N)

Lung transplant recipients and their matched comparison group subjects:

- a. Cumulative BCNU dose
- b. Cumulative CCNU dose
- c. Cumulative bleomycin dose
- c. Cumulative busulfan dose
- d. Cumulative cyclophosphamide dose
- e. Cumulative cis-platinum dose
- f. Methotrexate ≥ 24 gm/m² : (Y/N)
- g. Lung radiation (dose)
- h. Lung radiation + BCNU or CCNU: (Y/N)
- i. Lung radiation + bleomycin: (Y/N)
- j. Lung irradiation + busulfan: (Y/N)
- k. Total body irradiation: (Y/N)

Kidney transplant recipients and their matched comparison group subjects:

- a. Cumulative ifosfamide dose
- b. Cumulative cis-platinum dose
- c. Methotrexate > 24 gm/m² (Y/N)
- d. Abdominal irradiation (dose)
- e. Nephrectomy: (Y/N)
- f. Abdominal irradiation + nephrectomy : (Y/N)
- g. Abdominal irradiation + ifosfamide: (Y/N)

- h. Abdominal irradiation + cis-platinum: (Y/N)
- i. TBI: (Y/N)

Liver transplant recipients and their matched comparison group subjects:

- a. Cumulative actinomycin-d dose
- b. Cumulative methotrexate dose
- c. Cumulative cyclophosphamide dose
- d. Cumulative anti-metabolite dose = 6-mercaptopurine + 6-thioguanine dose
- e. Abdominal irradiation (right side) (dose)
- f. Abdominal irradiation (right side) + methotrexate: (Y/N)
- g. Abdominal irradiation (right side) + anti-metabolites (6-MP + 6-TG): (Y/N)
- h. TBI: (Y/N)
- i. Busulfan: (Y/N)
- j. Melphalan: (Y/N)

Statistical Analysis.

This will primarily be a descriptive study due to the small numbers of subjects who have received a solid organ transplant (Heart, n=29; Lung, n=4; Kidney, n=29; Liver, n=3; Total, n=66). The frequencies of death, recurrence of primary cancer and second malignant neoplasm events following SOT will be tabulated separately for recipients of each type of solid organ transplant (heart, lung, kidney, liver). Where the numbers of subjects in a group are sufficient (heart and kidney transplants only), the timing of outcome events following SOT will be summarized using cumulative incidence and survival curves. Overall curves for all SOT recipients combined will also be generated. Exposure to cancer therapy drugs with organ-specific toxicity potential and radiation exposure to the organ of interest will be summarized separately for recipients of each type of organ transplant.

While the sizes of the SOT groups are too small to support formal statistical hypothesis testing, it is nonetheless important to present an appropriate context in which to view the information on outcomes and treatment exposures for SOT cases. For this purpose, a similar set of descriptive summaries will be generated for matched survivors who did not undergo SOT. For the cumulative incidence and survival curve computations in the non-SOT group, the time origin for each subject will be set to correspond to the timing (relative to cancer diagnosis) of the organ transplant in the SOT case they were matched to.

Example of Specific Tables and Figures.

Table I. Demographic characteristics of 5-year survivors in the CCSS cohort undergoing Solid Organ Transplant.

	Heart	Lung	Kidney	Liver	All SOTs	Matched comparison group*
Age at diagnosis (yrs) (med, range)						
Age at Solid Organ Transplant (yrs)(med, range)						_____
Age at Follow-Up (Baseline,F/U 2007 or death) (yrs) (med, range)						
Time from diagnosis to Solid Organ Transplant (yrs)						_____
Gender (% male)						
Cancer Diagnosis N (%)						
Leukemia						
CNS						
HD						
NHL						
Wilms						
Neuroblastoma						
Bone sarcoma						
Soft Tissue Sarcoma						
Other						

* matched for gender, time under observation \geq time from dx to SOT for the corresponding SOT case, primary diagnosis, age at diagnosis within ± 5 years of the index SOT case

Table II. Treatment exposure in recipients of heart transplant and matched comparison subjects.

Treatment	Heart transplant subjects		Matched comparison subjects	
	Subjects that received (N, %)	Median dose and range	Subjects that received (N, %)	Median dose and range
Anthracyclines only				
Cyclophosphamide				
Heart Irradiation only				
Anthracycline plus Heart Irradiation		-----		-----
Cyclophosphamide plus Heart Irradiation		-----		-----
Cis-platinum				
TBI		-----		-----

Table III. Treatment exposure in recipients of lung transplant and matched comparison subjects.

Treatment	Lung transplant subjects		Matched comparison subjects	
	Subjects that received (N,%)	Median dose and range	Subjects that received (N,%)	Median dose and range
BCNU				
CCNU				
Bleomycin				
Busulfan				
Cyclophosphamide				
Cis-platin				
Methotrexate – > or = to 24 grams/m ²		-----		-----
Lung Irradiation only				
Lung Irradiation + BCNU or CCNU		-----		-----
Lung Irradiation + bleomycin		-----		-----
Lung Irradiation + busulfan		-----		-----
TBI		-----		-----

Table IV Treatment exposure in recipients of kidney transplant and matched comparison subjects

Treatment	Kidney transplant subjects		Matched comparison subjects	
	Subjects that received (N, %)	Median Dose and range	Subjects that received (N, %)	Median Dose and range
Nephrectomy		-----		-----
Ifosfamide				
Cis-platin				
Methotrexate (> or = to 24 grams/m ²)		-----		-----
Irradiation to Abdomen				
Abdominal Irradiation (any) + nephrectomy		-----		-----
Abdominal Irradiation (any) + ifosfamide		-----		-----
Abdominal Irradiation (any)+Cis-platin		-----		-----
TBI		-----		-----

Table V. Treatment exposure in recipients of liver transplant and matched comparison subjects.

Treatment	Liver transplant subjects		Matched comparison subjects	
	Subjects that received (N,%)	Median dose and range	Subjects that received (N,%)	Median dose and range
Actinomycin-D				
Methotrexate				
Anti metabolites				
Right side abdominal irradiation				
Right sided abdominal Irradiation (any) + methotrexate		-----		-----
Right sided abdominal Irradiation (any) +anti-metabolites		-----		-----
TBI		-----		-----
Cyclophosphamide				
Busulfan		-----		-----
Melphalan		-----		-----

Table VI. Follow-up on cohort participants reporting solid organ transplantation on Baseline questionnaire.

* if available

Transplant Type	Number of patients	Recurrence after Solid Organ Transplant	Second Malignancy after Solid Organ Transplant	Death Following Solid Organ Transplant	Cause of death*
Heart					
Lung					
Kidney					
Liver					
TOTAL					

Figures 1,2,3

K-M plots of survival, cumulative incidence of recurrence, and cumulative incidence of SMN with all SOT recipients combined; separate curves will be plotted for the matched nonSOT comparison group.

(technical notes: time origin for these plots will be time of transplant in the SOT group; subjects in the matched comparison group will have their t=0 set to correspond to the timing (relative to cancer diagnosis) of the organ transplant in the SOT case they were matched to)

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