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Survival of patients who develop solid tumors following hematopoietic stem cell transplantation

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Abstract

Allogeneic hematopoietic cell transplantation is associated with late adverse effects of therapy, including secondary solid cancers. Most reports address risk factors; however outcomes after secondary solid cancer development are incompletely described. Our objective was to estimate survival probabilities for transplant recipients dependent on secondary solid cancer subtype. We used a previously identified and published cohort who developed secondary solid cancers following allogeneic transplant. Follow-up for these 112 previously identified patients was extended and their survival probabilities were studied. Median duration of follow-up from the development of secondary cancer for survivors was 11.9 years (range: 0.8 – 23.4) and 75% were followed greater than 7.0 years. The 5- and 10-year overall survival probabilities were 50% (95% CI: 41 – 60%) and 46% (95% CI: 37 – 57%), respectively. Overall survival varied by secondary cancer type. Secondary cancer was the cause of death in most patients who died following development of melanoma, central nervous system, oral cavity, thyroid, lung, lower gastrointestinal tract, and bone cancers. Extended follow-up allowed for the most comprehensive longitudinal evaluation to date of this rare condition. These findings will enhance clinician ability to predict outcomes and counsel transplant survivors who develop secondary solid cancers.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) has become a widely accepted therapy for a variety of malignant and benign conditions. As utilization of HCT continues to increase, the number of transplants performed worldwide now exceeds 50 000 per year.

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Among these, more than 15 000 are performed yearly in the United States alone ([1]). With modern transplant approaches, over 85% of individuals surviving 2 years from the time of transplant will go on to experience long-term survival ([2–4]).

Improved survival after HCT has brought a realization of the many late-effects experienced by long-term survivors ([5–9]). Among the most significant late-effects are secondary cancers. Risk factors associated with the development of secondary cancers include genetic predispositions, age at the time of transplantation, use of total body irradiation (TBI), chronic graft-versus-host disease (GVHD), use of immunosuppressive therapy, and lifestyle factors ([10, 11]). Although much of the risk for secondary cancers is derived from transplant-related factors, development of secondary cancers likely results from the complex interaction between these various host, tumor, and environmental characteristics ([12]).

Risk for second cancers becomes apparent beginning at 5 years after transplant ([10, 11]). Several studies report incidences ranging from 2.2% to 6.4% at 10 years post-transplant ([13–18]). Two studies report cumulative incidences of 2.8% and 3.3% at 20 years post-transplant ([11, 17]). Outcomes for populations as a whole acquiring secondary malignancies have been described in the literature ([2, 14, 17]). These reports show patients with secondary solid cancers to have a 42–44% 5-year overall survival rate from the time of secondary cancer diagnosis ([14, 17]). The provided overall survival estimates are derived from studies containing between 19 and 55 patients with secondary solid cancers. There are no comprehensive reports describing mortality rates for specific subcategories of secondary solid tumors and therefore the significance of a particular diagnosis is unknown. Given that most individuals surviving beyond the first 2 years post-transplant will go on to experience excellent long term survival, a better understanding of the impact of secondary cancers on this group is needed ([2–4]). The current study therefore seeks to analyze survival after the diagnosis of a secondary solid cancer, using a well-characterized cohort of patients reported to the CIBMTR for whom the diagnosis of secondary cancer has been confirmed.

MATERIALS AND METHODS

Data Source

The CIBMTR collects transplant outcome data from patients at over 500 transplant centers worldwide. Longitudinal patient follow-up is collected on standardized data collection forms in a prospective manner until death or loss to follow-up and includes the occurrence of secondary malignancies. Compliance is monitored by routine on-site audits. All patients and/or their guardians are required to provide written informed consent. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Patients

This study provides extended follow-up on the cohort previously identified and published by Rizzo and colleagues ([11]). The original cohort was identified in order to describe the incidence of secondary solid cancers after allogeneic transplant. To achieve that aim, the cohort contained patients who received allogeneic bone marrow transplantations between

1964 and 1994 at participating CIBMTR transplant centers for a variety of malignant and nonmalignant indications. Those transplanted for Fanconi anemia or primary immunodeficiency diseases were excluded due to each condition's inherent susceptibility for cancer. Those without detailed information regarding HLA match, GVHD prophylaxis, and irradiation were excluded. The cohort was followed for the development of secondary solid cancers through 1995. Date of diagnosis, type of malignancy, site of occurrence, duration of follow-up, and outcome were recorded. Only those tumors for which the pathology and clinician reports underwent central review and reclassification for accuracy when necessary by the methods previously described were included ([11, 19]).

For the purpose of the current study, only those secondary cancers identified in the original study by Rizzo ([11]) were included. Extended follow-up of patients from the Fred Hutchinson Cancer Research Center was not available; therefore these patients have been excluded. We did not attempt to identify new secondary cancers, as the purpose of this study was to provide extended follow-up on previously validated secondary cancers. Follow-up of surviving patients was extended through 2014 to ascertain whether patients who were alive at close of previous study file were still alive. For deceased patients, date of death and the primary cause of death were obtained. The follow-up completeness indices at 5, 10, and 15 years were 100%, 97%, and 91%, respectively.

Study Objectives

The primary objective of this study was to describe survival following development of a secondary solid cancer, defined as death from any cause. A secondary objective was to describe the causes of death in this cohort.

Statistical Analysis

Descriptive statistics were used to summarize sample characteristics of those allogeneic transplant recipients who developed invasive secondary solid cancers. Individuals developing basal cell skin carcinomas and those whose secondary cancers were diagnosed at the time of autopsy were excluded from all survival analyses. For the purposes of outcomes analyses, secondary solid cancers were categorized into 14 groups: oral cavity and pharynx, lower gastrointestinal, liver, lung, bone, soft tissue, melanoma skin, non-melanoma skin, breast, female reproductive, male reproductive, central nervous system (CNS), thyroid, and miscellaneous/unknown primary cancers.

The probability of overall survival and median time from the development of a secondary solid cancer to death or last follow-up were calculated using the Kaplan-Meier estimator ([21]). Survival was calculated from the time of diagnosis of secondary solid cancer. Death from any cause was considered an event and data on patients alive at last follow-up were censored. The 95% confidence interval was calculated using log transformation. Median survival times were used to define stratified groups with similar overall survival rates. Cox proportional hazards model was used to evaluate the effect of lag time between transplant and the development of a secondary cancer on overall survival. Time dependent covariates were used to confirm that the proportional hazards assumption was met. The cumulative incidence of death from secondary solid cancer was estimated considering death from all

other causes as competing risk. A p-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Patients, Disease, and Transplant Characteristics

Among 23 471 patients who underwent allogeneic bone marrow transplantation, 146 new cases of solid cancers were observed at 68 treating institutions. These patients represent a subset of those considered by Rizzo and colleagues ([11]), as described in the methods above. Individuals developing basal cell skin carcinomas (n=28) and those whose secondary cancers were diagnosed at the time of autopsy (n=6) were excluded from further analysis in this study. Thus, there were 112 patients from 60 treating institutions evaluable for the current survival analysis (Figure 1). Among those diagnosed at autopsy (in all cases this was an incidental finding unrelated to the main reported cause of death), reported solid cancers included 1 clear cell carcinoma of the kidney, 1 metastatic neuroendocrine tumor of unknown primary, 1 malignant fibrous histiocytoma, 2 papillary thyroid carcinomas, and 1 squamous cell carcinoma of the lung (in situ). Patient, disease, and transplant characteristics are presented in Table 1. The most common indication for allogeneic transplantation was leukemia (78%). The donor source was an HLA-identical sibling for most (88%) transplants, and bone marrow the predominant graft. Most patients (75%) received transplant-conditioning regimen that included total body irradiation (TBI) and half (50%) reported chronic GVHD.

The characteristics of the 112 secondary solid cancers are shown in Table 2. There were 99 invasive solid cancers and 13 carcinomas in situ. Most (80%) secondary cancers were diagnosed 1 to 4 (43%) and 5 to 9 (37%) years post-transplant. No clear temporal pattern for the development of secondary cancers was evident among the different diseases.

The median duration of follow-up of the 112 patients, from the time of development of secondary cancer, was 11.9 years (range: 0.8 – 23.4). Seventy-five percent of patients were followed for more than 7 years, while 64% were followed for more than 15 years post-transplant.

Survival

Of the 112 patients evaluable for survival analysis, 65 have died. The median survival times and 5-year overall survival rates for individual cancer diagnoses are presented in Table 3. The overall survival probabilities at 1, 5, 10, and 15 years following development of an invasive or in situ secondary solid cancer was 73% (95% CI: 65 – 82%), 50% (95% CI: 41 – 60%), 46% (95% CI: 37 – 57%), and 40% (95% CI: 31–52%), respectively (Figure 2). Those who developed cancers of the male reproductive, thyroid, breast, and skin (melanoma) experienced the highest overall survival, with 5-year rates in excess of 70%. Conversely, those who developed cancers of the liver, lung, and CNS experienced 5-year overall survival rates lower than 10%.

Figure 3 represents the excess mortality risk for the study cohort when compared to the general population. From this figure we observe that after 6 years from secondary cancer diagnosis, the mortality rate of the study population is similar to that of the general population.

Regression analysis did not show a statistically significant increase in risk of death associated with longer time between transplant and secondary cancer diagnosis. More specifically, for each additional year from transplant to the secondary cancer diagnosis, the relative risk (RR) of mortality was 1.01 (95% CI: 0.94 – 1.08; p=0.72).

Cause of Death

The 5- and 10-year cumulative incidences of death due to secondary solid cancer were 12% and 26%, respectively, from the onset of secondary cancer (Figure 4). Secondary cancer was the most commonly reported cause of death for patients who died subsequent to the development of a secondary solid cancer. Among the 65 deaths in the study population, 41 (63%) were due to secondary cancer and 24 (37%) were due to other causes (5 (8%) deaths from graft versus host disease, 5 (8%) deaths from recurrent primary disease, 4 (6%) deaths from other causes, 3 (5%) deaths from unknown causes, 3 (5%) from organ failure, 2 (3%) deaths from infection, 1 (2%) death from interstitial pneumonitis, and 1 (2%) death from veno-occlusive disease). Secondary cancer was the leading cause of death for those patients who died at any time point (including beyond 5 years) following the development of CNS (n=9/9, 100%), lung (n=4/4, 100%), thyroid (n=1/1, 100%), miscellaneous/unknown primary (n=4/5, 80%), bone (n=3/4, 75%), oral cavity (n=5/7, 71%), melanoma (n=3/5, 60%), and lower GI tract (n=3/5, 60%) secondary solid cancers.

DISCUSSION

This study extends follow-up on our previously identified cohort and provides more complete characterization of the survival patterns for this group. The 50% 5-year overall survival for this cohort is slightly higher than previously described in other studies, likely due to our inclusion of in situ carcinomas ([14], [17]). However, our study demonstrates that the highest risk for mortality after secondary cancer occurs primarily within the first 5 years after secondary cancer diagnosis, as evidenced by 10- and 15-year overall survival estimates of 46% and 40%, respectively. Additionally, we identified solid cancers for which mortality rates approached 100% within 5 years from diagnosis. Knowledge of the likely outcome from an individual diagnosis of malignancy may be helpful for both patients and providers when balancing decisions between treatment intensity and quality of life planning.

This study additionally describes outcomes of allogeneic transplant survivors specific to the types of secondary solid cancers they developed. Overall survival was particularly poor for those patients who developed secondary solid cancers of the CNS, liver, and lung. The median survival time was 6 months or less from diagnosis of secondary cancer, and nearly all died within 15 years from transplant, sharply contrasting the 75% 15-year overall survival rate anticipated by others surviving ≥2 years post-transplant who have not developed secondary cancers ([2], [4]). Secondary cancer was the cause of death for the majority (86%) of these individuals. This group represents a cohort of patients with an exceptionally poor

outcome, consistent with that of their *de novo* counterparts. Thus, close secondary cancer surveillance remains a crucial component of long-term follow-up for allogeneic transplant survivors ([22]).

Conversely, greater than 50% of the patients who developed male reproductive, thyroid, breast, and skin (melanoma) cancers were alive at the time of last follow-up. Among those who died following any of these diagnoses, secondary cancer was the cause of death in 63%. Whether the improved survival in these patients is reflective of current screening practices and shorter time to detection, more effective treatment regimens, or less aggressive tumor biology remains unclear. Figure 5 depicts the 5-year survival rates for specific secondary solid cancer groups with respect to their de novo counterpart taken from the Surveillance, Epidemiology, and End Results (SEER) data ([23]). It should be noted that the figure reflects only observational comparisons. In general, however, the 5-year survival rates for most secondary solid cancers appear comparable to similar *de novo* cancers. Notable exceptions include female reproductive, bone and joint, lower GI tract, and CNS tumors. These observed differences suggest a group of tumors that may have worse survival outcomes when developing as a secondary malignancy. Several explanations may explain these differences: 1) aggressive cancers in a heavily pretreated population may portend a worse prognosis; 2) time to secondary cancer development may impact survival following diagnosis; 3) stage at presentation may differ between *de novo* and secondary solid cancers; 4) tumor responsiveness to therapy may be worse for secondary cancers; or 5) these findings may simply represent our sample size limitations. Despite our robust cohort, the inability to determine second cancer stage, treatment, and existing comorbidities present at the time of secondary cancer diagnosis precludes the ability to perform meaningful statistical comparisons to primary cancers in the general population.

Transplant related risks factors which have been associated with the development of secondary solid cancers include age at the time of transplantation, use of total body irradiation, chronic GVHD, and use of immunosuppressive therapy ([10], [11]). Specifically, irradiation has been shown to increase the risk for non-squamous cell carcinomas while chronic GVHD appears to increase the risk of squamous cell carcinomas. Among patients with secondary cancers in our study in whom survival is poorest, only those of CNS, bone, and soft tissue have been shown to be significantly associated with radiation exposure ([11]). Given the limitations of these data, we cannot determine any association between previous irradiation and prognosis following the development of a secondary solid cancer.

These findings have several limitations. First, this study is subject to the limitations common to all retrospective, observational cohort studies. While outcomes registries represent an excellent resource to evaluate rare late effects of treatment, there is a risk of under-reporting of rare events due to loss to follow-up, which would serve to underestimate incidence and possibly over-estimate survival. Second, even in this large cohort, relatively small numbers of specific tumor types exist. Interpretation of the overall survival for specific tumor types should be made with caution, however, as we do not know whether individuals were treated or not, and thus what subsequent impact this decision had on overall survival. The limited sample size and heterogeneity of the cohort preclude the ability to reasonably investigate the impact of treatment related factors on overall survival. Finally, we describe second cancers

and subsequent outcomes in a patients transplanted before 1995. While transplant approaches and treatments have changed, and patients undergoing HCT in a more recent cohort may have different specific exposures and cancer risk, the outcomes for this historic cohort provide generalizable guidance for subsequent cohorts of recipients who develop second malignancies.

In conclusion, we report a large cohort of allogeneic transplant survivors who develop secondary solid malignancies. Utilization of the large CIBMTR cohort allows for more representative longitudinal evaluation of an otherwise uncommon condition. In particular, we are able to show long term survival rates for each tumor type. These findings will enhance the ability of clinicians to predict outcomes and subsequently counsel transplant survivors who develop secondary solid cancers.

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Figure 1.
Patient selection.

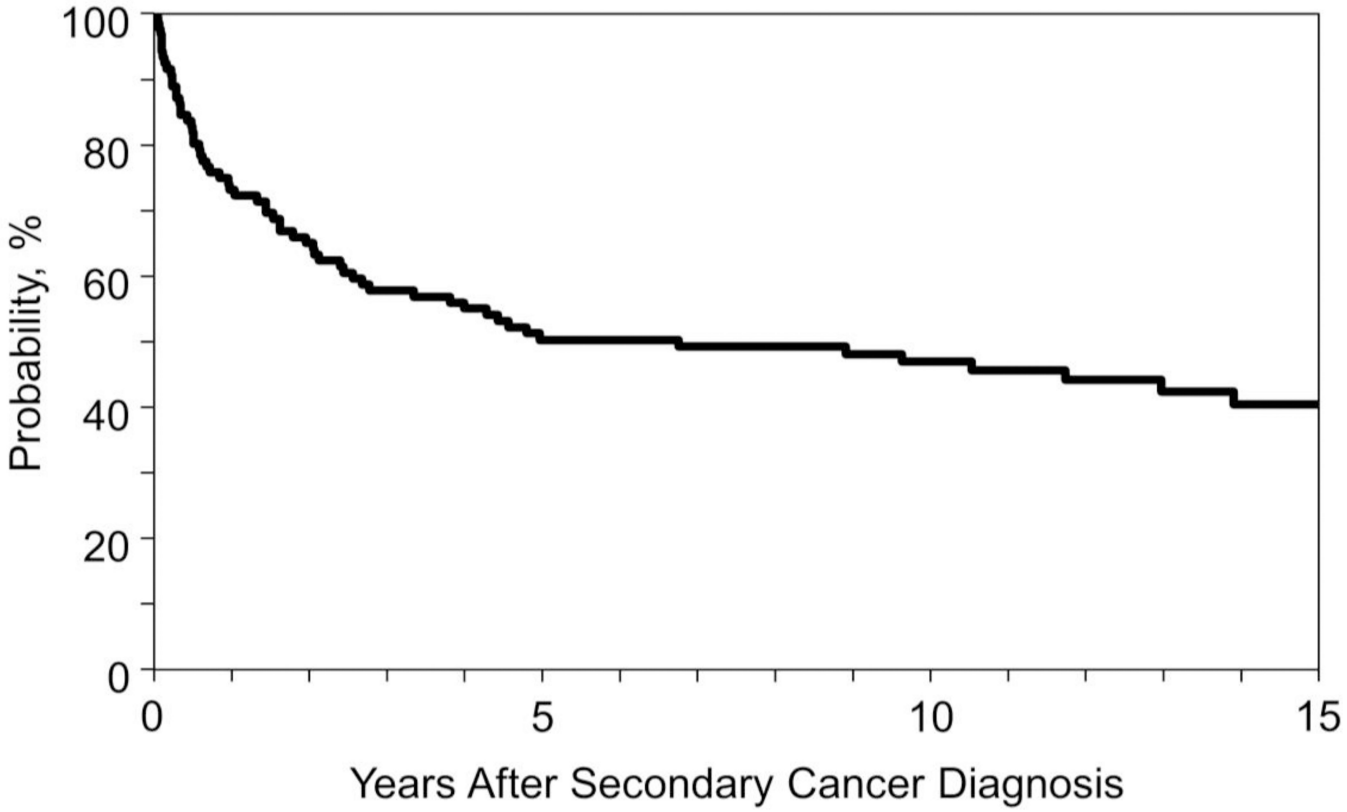

Figure 2.
Probability of overall survival for entire cohort.

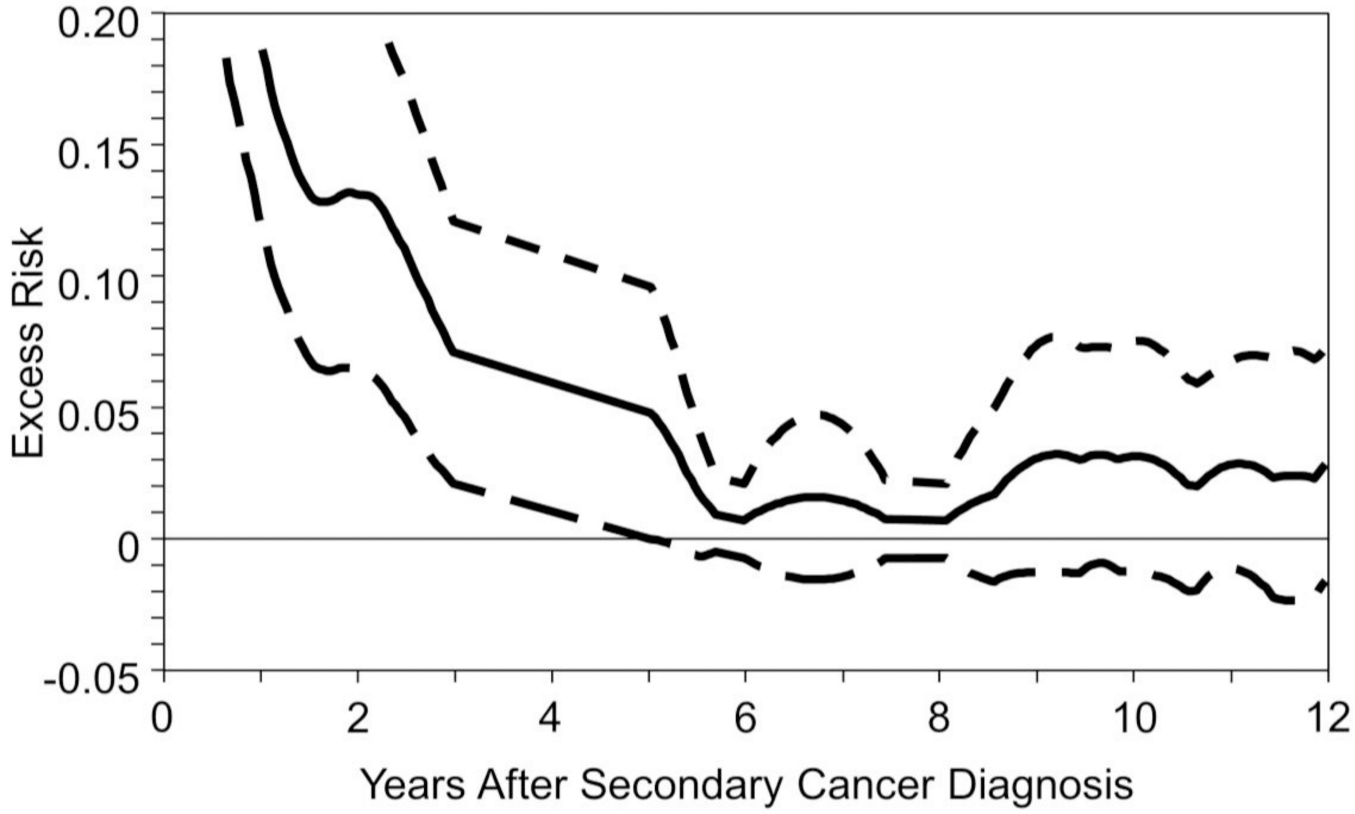

Figure 3.
Estimated excess mortality risk with 95% confidence interval for those with a secondary solid cancer compared to the general population.

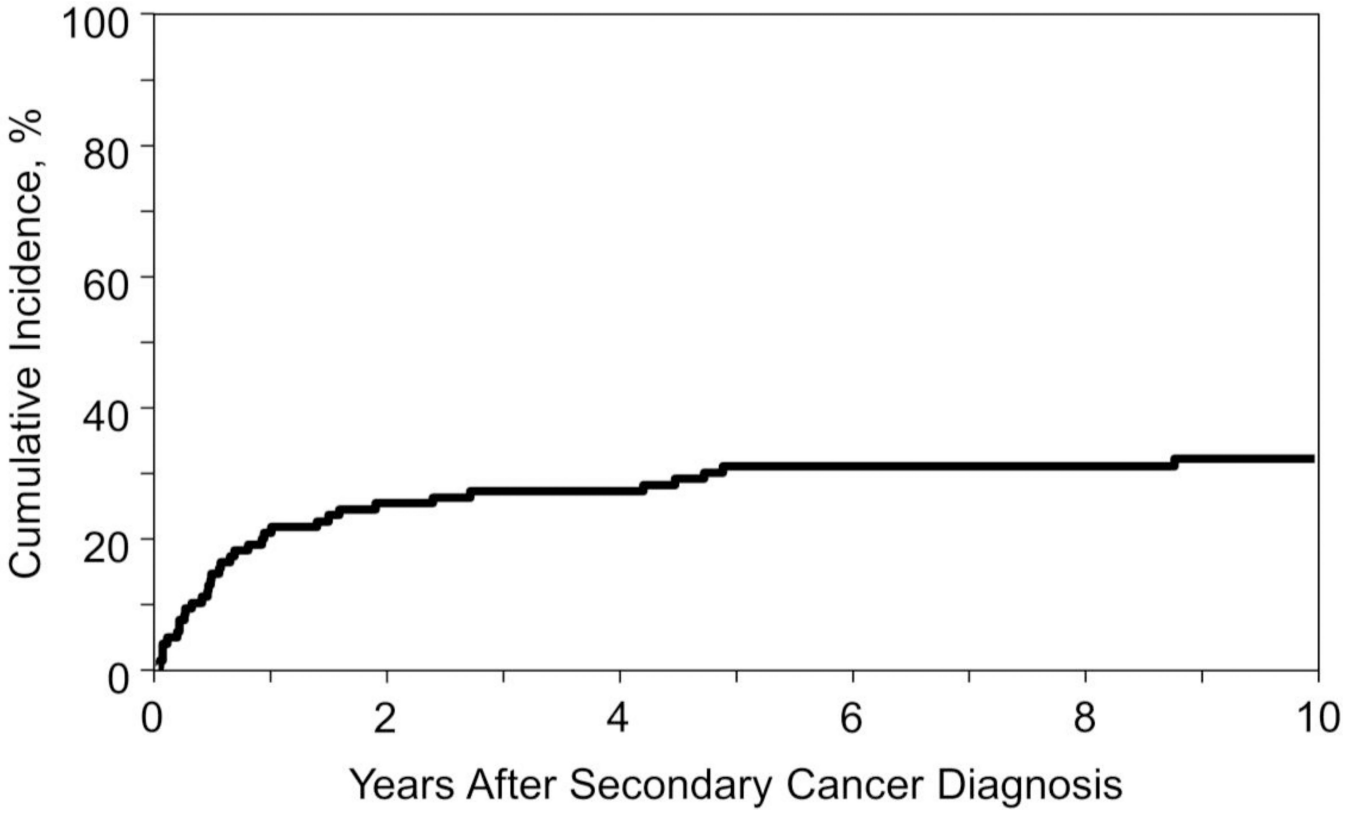

Figure 4.
Cumulative incidence of death due to secondary solid cancer.

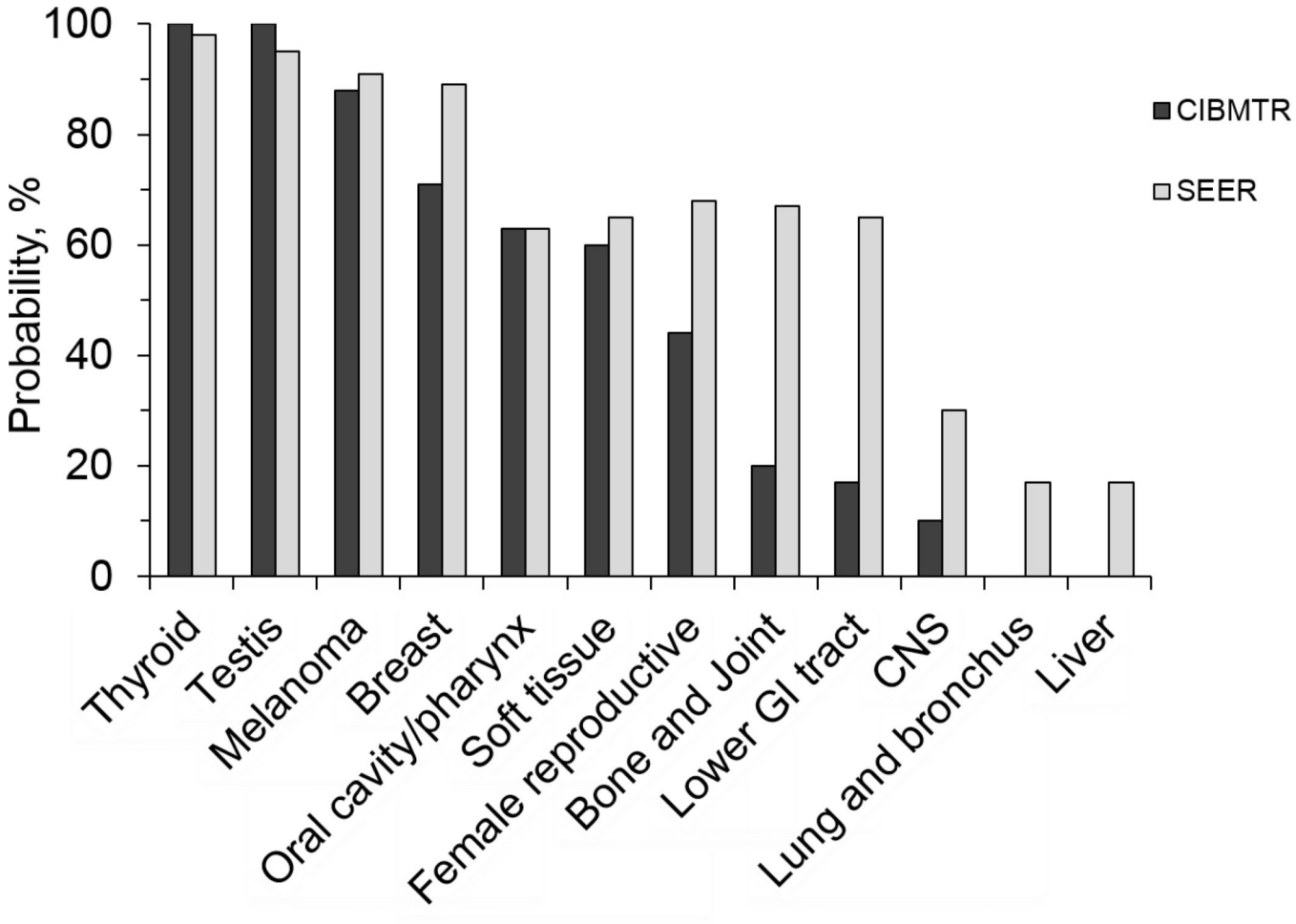

Figure 5.
Observational comparison of the probability of 5-year overall survival for secondary and *de novo* solid cancers (SEER data). Formal statistical comparison not performed.

Table 1

Characteristics of patients who developed secondary solid cancers

Characteristic	N (%)
Number of patients	112
Number of centers	60
Sex	
Male	61 (54)
Female	51 (46)
Age at transplant	
0–9	15 (13)
10–19	15 (13)
20–29	28 (25)
30–39	25 (23)
40–49	22 (20)
50 or older	7 (6)
Primary disease	
ALL	14 (12)
ANLL	40 (35)
CML	28 (25)
Other leukemia	4 (4)
NHL	5 (4)
MM	2 (2)
Other malignancy	2 (2)
MDS	2 (2)
SAA	13 (12)
Hemoglobinopathies	2 (2)
Donor type	
Identical twin	1 (1)
HLA-identical sibling	98 (88)
HLA-mismatched sibling, other relative	7 (6)
Unrelated	6 (5)
Conditioning regimen	
TBI + Cy ± other drugs	78 (70)
TBI + other drugs (No Cy)	6 (5)
LFI ± CY ± other drugs	7 (6)
Bu + Cy ± other drugs	16 (14)
Cy ± other drugs	4 (4)
Other	1 (1)
GVHD prophylaxis	
T-cell depletion	17 (16)
CSA + MTX	33 (29)
CSA (no MTX)	29 (26)

Characteristic	N (%)
MTX (no CSA)	33 (29)
TBI dose	
No TBI or TLI	21 (19)
TLI only	7 (6)
Single dose	27 (24)
Fractionated dose, less than 12 Gy	13 (12)
Fractionated dose, 12 Gy to less than 14 Gy	36 (32)
Fractionated dose, 14 Gy or more	8 (7)

ALL indicates acute lymphoblastic leukemia; ANLL, acute nonlymphocytic leukemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; MDS, myelodysplastic syndromes; and SAA, severe aplastic anemia. HLA indicates human leukocyte antigen. TBI indicates total body irradiation; Cy, cyclophosphamide; CsA, cyclosporine; MTX, methotrexate; and TLI, total lymphoid irradiation.

Table 2

Characteristics of the secondary solid cancers (N=112)

Cancer subgroup	Site	Behavior	N	(%)
Melanoma skin			16	(14)
Melanoma	-	In situ	2	
Melanoma	-	Invasive	14	
Non-melanoma skin			15	(14)
Basosquamous carcinoma	-	Invasive	2	
Squamous cell carcinoma	-	In situ	3	
Squamous cell carcinoma	-	Invasive	7	
Spinocellular carcinoma	-	Invasive	2	
Other	-	In situ	1	
Central nervous system			10	(9)
Astrocytoma	Brain	Invasive	2	
Astrocytoma	Spinal cord	Invasive	1	
Glioblastoma multiforme	Brain	Invasive	6	
Primitive neuroectodermal tumor	Brain	Invasive	1	
Oral cavity			14	(13)
Squamous cell carcinoma	Gum, other mouth	Invasive	2	
Squamous cell carcinoma	Lip	Invasive	3	
Squamous cell carcinoma	Hypopharynx	Invasive	1	
Squamous cell carcinoma	Tongue	Invasive	5	
Spinocellular carcinoma	Lip	Invasive	1	
Mucoepidermoid carcinoma	Parotid	Invasive	2	
Thyroid			8	(7)
Malignant adenoma	-	Invasive	1	
Papillary carcinoma	-	Invasive	7	
Lung			4	(4)
Adenocarcinoma	Lung/bronchus	Invasive	2	
Squamous cell carcinoma	Pleura	Invasive	1	
High grade sarcoma	Lung	Invasive	1	

Cancer subgroup	Site	Behavior	N	(%)
Breast			7	(6)
Adenocarcinoma	-	In situ	2	
Adenocarcinoma	-	Invasive	5	
Liver			4	(4)
Angiosarcoma	-	Invasive	1	
HCC	-	Invasive	2	
Malignant fibrous histiocytoma	-	Invasive	1	
Lower gastrointestinal tract			6	(5)
Adenocarcinoma	Rectum	In situ	1	
Adenocarcinoma	Colon	Invasive	2	
Leiomyosarcoma	Small intestine	Invasive	1	
Squamous cell carcinoma	Anus	In situ	1	
Squamous cell carcinoma	Rectum	Invasive	1	
Female reproductive			9	(8)
Adenocarcinoma	Uterus (endometrium)	Invasive	1	
Carcinoma	Cervix	In situ	1	
Carcinoma, NOS	Cervix	Invasive	1	
Carcinoma, NOS	Vulva	Invasive	1	
Desmoplastic round cell tumor	Uterus	Invasive	1	
Intraepithelial neoplasia	Cervix	In situ	2	
Rhabdomyosarcoma	Cervix	Invasive	1	
Squamous cell carcinoma	Cervix	Invasive	1	
Male reproductive			2	(2)
Seminoma	Testes	Invasive	2	
Bone			5	(4)
Chondrosarcoma	Tibia	Invasive	1	
Chondrosarcoma	Ischium	Invasive	1	
Osteosarcoma	Face	Invasive	1	
Osteocarcinoma	Tibia	Invasive	1	
Sarcoma, NOS	Iliac wing	Invasive	1	
Soft tissue			5	(4)

Cancer subgroup	Site	Behavior	N	(%)
Ewing sarcoma	Thigh	Invasive	1	
Fibrosarcoma	Neck	Invasive	1	
Malignant peripheral nerve sheath tumor	Thigh	Invasive	1	
Malignant fibrous histiocytoma	Pectorus	Invasive	1	
Rhabdomyosarcoma	Thigh	Invasive	1	
Miscellaneous/Unknown primary			7	(6)
Kaposi sarcoma	Stomach/esophagus	Invasive	1	
Kaposi sarcoma	Skin/leg	Invasive	1	
Metastatic andenocarcinoma, unknown primary	Pleura	Invasive	2	
Metastatic carcinoma, unknown primary	Thoracic spine	Invasive	1	
Squamous cell carcinoma	Penis	Invasive	1	
Transitional cell carcinoma	Bladder	Invasive	1	

Excludes 6 secondary cancers diagnosed at autopsy (squamous cell carcinoma of lung, in situ [n=1]; clear cell carcinoma of kidney, invasive [n=1]; metastatic neuroendocrine tumor of unknown primary, invasive [n=1]; malignant fibrous histiocytoma of liver, invasive [n=1]; papillary thyroid carcinoma, invasive [n=2]).

Table 3

Median survival from time of second cancer development

Cancer	N	Median survival (years)	5-Year overall survival, % (95% confidence interval)
Male reproductive	2	-	100
Thyroid	8	-	100
Breast	7	-	71 (45–100)
Soft tissue	5	-	60 (29–100)
Melanoma skin	16	20.1	88 (73–100)
Oral cavity	14	13.7	64 (42–95)
Non-melanoma skin	15	4.5	47 (27–80)
Lower gastrointestinal tract	6	2.6	17 (3–100)
Bone	5	2.4	20 (4–100)
Female reproductive	9	2.0	44 (21–92)
Central nervous system	10	0.5	10 (2–64)
Miscellaneous/unknown primary †	7	0.5	29 (9–92)
Lung	4	0.4	0
Liver	4	0.1	0

†Miscellaneous/unknown primary cancers included Kaposi sarcoma (n=2), metastatic adenocarcinoma of unknown primary (n=2), metastatic carcinoma of unknown primary (n=1), squamous cell carcinoma of the penis (n=1), and transitional cell carcinoma of the bladder (n=1).