Patterns of Cancer Care and Association with Survival among Younger Adolescents and Young Adults: A Population-Based Retrospective Cohort Study

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ABSTRACT

Background: Younger adolescents and young adults (AYA) may receive care from either adult or pediatric oncologists. We explored patterns of care in this population and whether survival is associated with provider type.

Methods: Utilizing the California Cancer Registry, we examined a cohort of 9,993 AYAs diagnosed with cancer aged 15 to 24 years from 1999 to 2008. Provider type (adult/pediatric) was determined by individual physician identifiers. For provider type, multivariable logistic regression models were adjusted for age, sex, race/ethnicity, socioeconomic status, diagnosis, and stage. For observed survival, Cox proportional hazard models were additionally adjusted for provider type. ORs and HR with 95% confidence intervals (95% CI) were determined.

Results: Most patients saw adult providers (87.3% overall; 72.7% aged 15–19 years). Patients with acute leukemia, sarcoma, and central nervous system (CNS) malignancies more often saw pediatric providers [OR (95% CI) adult versus pediatric 0.48 (0.39–0.59), 0.74 (0.60–0.92), 0.76 (0.60–0.96), respectively]; those with germ cell tumors and other cancers, including carcinomas, more often saw adult providers [2.26 (1.72–2.98), 1.79 (1.41–2.27), respectively]. In aggregate and for most cancers individually, there was no survival difference by provider type [overall HR (95% CI) 1.00 (0.86–1.18)]. Higher survival was associated with pediatric providers for CNS malignancies [1.63 (1.12–2.37)] and rhabdomyosarcoma [2.22 (1.03–4.76)], and with adult providers for non-Hodgkin lymphoma [0.61 (0.39–0.96)].

Conclusions: Most AYAs 15 to 24 years old are treated by medical oncologists. In general, survival was not associated with provider type.

Impact: Current patterns of care for this population support increased collaboration between medical and pediatric oncology, including joint clinical trials.

Introduction

Being at the cusp of pediatric and adult medicine, adolescents and young adults (AYA) diagnosed with cancer between 15 and 24 years of age may access either adult or pediatric oncology care. Studies indicate that oncology provider type for AYAs varies by age and diagnosis. There is a steep decline in referral to pediatrics beginning about 14 years old and most AYAs aged 15 to 19 years are treated by adult providers (1–6). Data suggest that younger AYAs with acute leukemia and sarcomas tend to see pediatric providers, whereas those with germ cell tumors (GCT) and carcinomas more often access adult providers (1, 3, 5, 6). However, neither subspecialty is specifically trained nor focused on the entire AYA population, and for certain common AYA cancers, adult and pediatric oncologists follow different treatment paradigms. Whether and to what degree provider type affects survival in this population remains unclear.

Several studies have shown that AYAs with acute lymphoblastic leukemia (ALL) achieve better survival with pediatric-based regimens (7–15), leading to treatment recommendations incorporating pediatric approaches (15). Similarly, pediatric-based treatment has been associated with improved survival for AYAs with Ewing sarcoma (16, 17), rhabdomyosarcoma (18, 19), Hodgkin lymphoma (20), and acute myeloid leukemia (AML; ref. 21). In a population-based study of AYAs aged 15 to 19 years treated at Children's Oncology Group (COG) member and non-member institutions in Georgia (3), survival trends suggested that young AYAs with "pediatric-type" cancers benefit from treatment by pediatric oncologists, while those with "adult-type" cancers fare better with adult oncologists (3, 22). A similar study limited to AYAs aged 15 to 21 years with melanoma and carcinomas showed no survival difference for patients treated at adult versus pediatric centers (2).

Further, AYAs are evaluated at presentation by varied providers, including pediatricians, internists, family physicians, gynecologists, surgeons, and emergency physicians (23), resulting in referral patterns more dependent on the specialty of the referring provider, available resources, insurance requirements, and local practices than on objective clinical factors (5, 24). Additionally, most AYAs are treated outside specialized cancer centers (25, 26). Given the currently unsettled but important question of how oncology provider type may impact outcomes of AYAs, we conducted this population-based study to (i) establish the proportions of AYAs 15 to 24 years old with cancer that were treated by adult or pediatric oncology providers in California, and

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(ii) determine if provider type influenced survival. Our central hypothesis was that certain diagnostic subgroups would differentially benefit from referral to either adult or pediatric oncology providers. Our overall objectives were to gain insights regarding optimal care of younger AYAs with common cancers and to elucidate opportunities for greater collaboration between pediatric and medical oncology in AYA cancer care and research.

Materials and Methods

Data source

Since 1988, the California Cancer Registry (CCR) has collected demographic and disease-specific information on all incident cases of cancer among state residents within 6 months of diagnosis. The three regional registries that comprise the CCR are NCI-designated Surveillance Epidemiology and End Results (SEER) registries. Demographic information includes age at diagnosis, sex, race/ethnicity, and a US census-tract based estimate of socioeconomic status (SES) based on residence at diagnosis. The census tracts were categorized into quintiles based on the SES score. Vital status is ascertained annually through hospital contact and linkages with state vital records and the National Death Index. Disease-specific information includes date of diagnosis, site, histology, and stage. Available treatment information includes treatment site(s), treating physician(s), and limited details regarding initial inpatient therapy.

Study cohort and measures

Incident cancers diagnosed in California from January 1, 1999 to December 31, 2008 among patients aged 15 to 24 were included. Excluded were cancer types routinely treated by other specialists, including melanoma and thyroid, cervical, endometrial, ovarian, or skin carcinoma; Kaposi sarcoma as epidemiologically distinct from other sarcomas; relapse from an initial diagnosis made before the study period; second malignant neoplasm; and cases diagnosed at autopsy only. Cancer diagnoses were subdivided by site according to the AYA Site Recode and World Health Organization 2008 definition.

The CCR collects state medical license numbers of physician(s) involved in the diagnosis and treatment of each patient. Physician type was coded as a binary variable (adult or pediatric). In cases where more than 1 physician was listed, a predefined algorithm was used to identify the medical or pediatric oncologist, followed by the attending physician, surgeon, or other doctors in a specified order. Data on physicians ever licensed in California, including subspecialty, are publicly available through a state-administered website. Physicians with any pediatric designation were coded as pediatric and all others as adult.

In California, 19 institutions are affiliated with the COG, and account for 4.8% of hospitals statewide. Patients treated at COG institutions that report their pediatric and adult cases jointly to the CCR were coded for provider type using the preceding methodology. Patients from COG institutions that are free-standing children's hospitals and report their cases separately from any affiliated adult hospitals were coded as having pediatric providers. Patients from COG member institutions without treating physician data were coded as unknown. Patients from institutions with no COG affiliation were coded as having adult providers.

Statistical analysis

Baseline patient characteristics were compared by physician type (adult, pediatric, unknown) using the χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables.

Multivariable logistic and Cox regression analyses were used to determine factors associated with two outcomes: (i) physician specialty (adult or pediatric) and (ii) observed survival. For both outcomes, independent variables included age (continuous), sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, other), SES [by quintiles, 1 (lowest) through 5 (highest)], stage (non-metastatic, metastatic, unknown), and cancer diagnosis [lymphoma, extracranial GCT, sarcoma, acute leukemia, central nervous system (CNS) malignancies, other]. These variables were determined *a priori* and included in all models as potentially relevant.

Two multivariable logistic models were used to examine the effects of stage and diagnosis on physician type. The first model excluded stage in order to examine the effect of cancer diagnosis, as all leukemia cases are coded as metastatic. The second model excluded all leukemia cases in order to examine the effect of stage, which is applicable only to solid tumors. Odds ratios (OR) with 95% confidence intervals (CI) were computed.

For survival, the same independent variables were included *a priori* in building all multivariable models; physician type (adult or pediatric) was retained throughout. Survival time was calculated as interval from the date of diagnosis to the date of death. Patients lost to follow-up or alive on December 31, 2008, were censored at the date of last known follow up. For survival of the entire cohort, leukemia was excluded in order to adjust for cancer stage and diagnosis was aggregated into six major diagnostic categories (lymphoma, extracranial GCT, sarcoma, CNS malignancies, carcinoma, and other). Models for lymphoma, sarcoma, acute leukemia, and CNS malignancies were additionally adjusted for diagnostic subtypes within each of these categories. Multivariable survival models were also built for individual cancer diagnoses where the number of patients seen by pediatric providers was deemed sufficient (non–Hodgkin and Hodgkin lymphoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, ALL, and AML; **Table 1**). HRs and associated 95% CI were calculated from these models. The Cox proportional hazards assumption was evaluated using Schoenfeld residuals and log–log plots. Significant nonproportionality of hazards was present and time interaction terms were retained in the model. Direct adjusted survival curves were created in SAS using the proportional hazards command (PROC PHREG), using the full multivariable model with the BASELINE statement and DIRADJ option (27). Model diagnostics using DFBETAS panels were conducted to exclude the possibility of influential observations arising from longer-term survivors (28). Unadjusted survival estimates at 3, 5, and 8 years were generated using the Kaplan Meier method. All P values are two-sided with statistical significance set to $P < 0.05$. All statistical analyses were performed utilizing SAS software (version 9.4; SAS Institute Inc).

Results

Patient characteristics

For the entire cohort ($n = 9{,}993$; **Table 2**), there was a male predominance ($n = 6{,}205$, 62.1%); the median age ± SD was 20 ± 2.9 years; most were non-Hispanic white ($n = 4{,}223$, 42.3%) or Hispanic ($n = 4{,}002$, 40.1%); the distribution by SES quintile was approximately even; and approximately one quarter presented with metastases ($n = 2{,}431$, 27.7%). Lymphoma and extracranial GCT were the most common diagnoses (26.4% and 21.1%, respectively).

Patients treated by pediatric providers were significantly younger than those treated by adult providers (16 ± 1.7 years vs. 21 ± 2.7 years, respectively; $P < 0.01$), more likely to be Hispanic (43.6% vs. 40.0%;

Table 1. Distribution of specific cancers[a] by provider type among AYAs 15 to 24 years old (CCR, 1999–2008).

Diagnosis	Total	Adult			Pediatric			Unknown		
	n	*n*	%[b]	%[c]	*n*	%[b]	%[c]	*n*	%[b]	%[c]
Total	9,993	8,507	85.1	—	1,242	12.4	—	244	2.5	—
Lymphoma	2,633	2,302	87.4	27.1	278	10.6	22.4	53	2.0	21.7
Hodgkin	1,652	1,458	88.3	63.3	161	9.7	57.9	33	2.0	62.3
Non–Hodgkin	981	844	86.0	36.7	117	11.9	42.1	20	2.1	37.7
Extracranial GCT	2,111	1,969	93.3	23.1	87	4.1	7.0	55	2.6	22.5
Gonadal	1,958	1,833	93.6	93.1	73	3.7	83.9	52	2.7	94.5
Non-gonadal	153	136	88.9	6.9	14	9.1	13.8	3	2.0	5.5
Sarcoma – soft tissue	756	643	85.1	7.6	94	12.4	7.6	19	2.5	7.8
Other	337	291	86.3	45.2	38	11.3	40.4	8	2.4	42.1
Fibromatous	212	195	92.0	30.3	13	6.1	13.8	4	1.9	21.1
Rhabdomyosarcoma	113	81	71.7	12.6	27	23.9	28.7	5	4.4	26.3
NOS	94	76	80.9	11.8	16	17.0	17.0	2	2.1	10.5
Sarcoma – bone	632	455	72.0	5.3	163	25.8	13.1	14	2.2	5.7
Osteosarcoma	324	229	70.7	50.3	89	27.5	54.6	6	1.8	42.9
Ewing sarcoma	210	144	68.6	31.6	59	28.1	36.2	7	3.3	50.0
Chondrosarcoma	52	46	88.5	10.1	5	9.6	3.1	1	1.9	7.1
NOS and other	46	36	78.3	7.9	10	21.7	6.1	—	—	—
Acute leukemia	1,206	870	72.1	10.2	310	25.7	25.0	26	2.2	10.7
Lymphoblastic	761	518	68.1	59.5	224	43.2	72.3	19	3.7	73.1
Myeloid	445	352	79.1	40.5	86	19.3	27.7	7	1.6	26.9
CNS malignancy	1,041	831	79.8	9.8	176	16.9	14.2	34	3.3	13.9
Low-grade astrocytoma	240	186	77.5	22.4	45	18.7	25.6	9	3.8	26.5
Glioma, other	176	157	89.2	18.9	15	8.5	8.5	4	2.3	11.8
High-grade astrocytoma	162	132	81.5	15.9	23	14.2	13.1	7	4.3	20.6
GCT	124	90	72.6	10.8	31	25.0	17.6	3	2.4	8.8
Astrocytoma, NOS	112	85	75.9	10.2	22	19.6	12.5	5	4.5	14.7
Medulloblastoma	84	69	82.1	8.3	13	15.5	7.4	2	2.4	5.9
Supratentorial PNET	77	58	75.3	7.0	18	23.4	10.2	1	1.3	2.9
Ependymoma	66	54	81.9	6.5	9	13.6	5.1	3	4.5	8.8
Carcinoma	1,022	946	92.6	11.1	47	4.6	3.8	29	2.8	11.9
Colorectal	214	206	96.2	21.8	1	0.5	2.1	7	3.3	24.1
Other, oropharynx	158	151	95.5	16.0	4	2.6	8.5	3	1.9	10.3
Breast	134	132	98.6	14.0	1	0.7	2.1	1	0.7	3.4
Lung	81	69	85.2	7.3	8	9.9	17.0	4	4.9	13.8
Liver/biliary	72	55	76.4	5.8	15	20.8	31.9	2	2.8	6.9
Renal cell	70	67	95.8	7.1	2	2.8	4.2	1	1.4	3.4
Nasopharyngeal	67	58	86.5	6.1	5	7.5	10.6	4	6.0	13.8
Other	51	41	80.4	4.3	8	15.7	17.0	2	3.9	6.9
Stomach	44	43	97.7	4.5	—	—	—	1	2.3	3.4
Pancreatic	33	29	87.9	3.1	2	6.1	4.2	2	6.1	6.9
Other, head/neck	22	22	100.0	2.3	—	—	—	—	—	—
Other, gastrointestinal	20	20	100.0	2.1	—	—	—	—	—	—
Other, genitourinary	20	19	95.0	2.0	—	—	—	1	5.0	3.4
Bladder	15	15	100.0	1.6	—	—	—	—	—	—
Adrenocortical	14	12	85.7	1.3	1	7.1	2.1	1	7.1	3.4
Gonadal, testicular	7	7	100.0	0.7	—	—	—	—	—	—
Other	592	491	82.9	5.8	87	14.7	7.0	14	2.4	5.7
Chronic myeloid leukemia	175	141	80.6	28.7	27	15.4	31.0	7	4.0	50.0
Neoplasms, other	142	121	85.2	24.6	20	14.1	23.0	1	0.7	7.1
Leukemia, NOS and other	72	61	84.7	12.4	10	13.9	11.5	1	1.4	7.1
Myeloma	41	34	82.9	6.9	7	17.1	8.0	—	—	—
Neoplasms, NOS	36	35	97.2	7.1	1	2.8	1.1	—	—	—
Intracranial/intraspinal, other	31	26	83.9	5.3	4	12.9	4.6	1	3.2	7.1
Paraganglioma and glomus	23	18	78.3	3.7	3	13.0	3.4	2	8.7	14.2
Gonadal, other	20	17	85.0	3.5	2	10.0	2.3	1	5.0	7.1
Other pediatric/embryonal	18	11	61.1	2.2	6	33.3	6.9	1	5.6	7.1
Neuroblastoma	11	10	90.9	2.0	1	9.1	1.1	—	—	—
Intracranial/intraspinal, NOS	10	10	100.0	2.0	—	—	—	—	—	—
Unclassified	7	3	42.9	0.6	4	57.1	4.6	—	—	—
Wilms	6	4	66.7	0.8	2	33.3	2.3	—	—	—

Abbreviation: NOS, not otherwise specified.

[a]Cancers excluded from analysis: melanoma, thyroid, cervical, endometrial, ovarian, and skin carcinoma, Kaposi sarcoma (see Methods).

[b]Row percentages (distribution between provider types).

[c]Column percentages (distribution within provider type).

Table 2. Characteristics of AYAs (15–24 years old) newly diagnosed with cancer, by provider type (CCR, 1999–2008).

	Total population (%)	Adult (%[a])	Pediatric (%[a])	Unknown (%[a])	*P*
Number	9,993	8,507 (85.1)	1,242 (12.4)	244 (2.5)	—
Age (median, SD)	20 ± 2.9	21 ± 2.7	16 ± 1.7	20.6 ± 2.5	<0.01
Sex					
Male	6,205 (62.1)	5,277 (62.0)	755 (60.8)	173 (70.9)	0.40
Female	3,788 (37.9)	3,230 (38.0)	487 (39.2)	71 (29.1)	
Race/ethnicity					
Non-Hispanic white	4,223 (42.3)	3,624 (42.6)	471 (37.9)	128 (52.4)	<0.01
Non-Hispanic black	595 (5.9)	497 (5.8)	77 (6.2)	21 (8.6)	
Hispanic	4,002 (40.0)	3,400 (40.0)	541 (43.6)	61 (25)	
Asian/Pacific	995 (10.0)	828 (9.7)	140 (11.3)	27 (11.1)	
Other	178 (1.8)	158 (1.9)	13 (1.0)	7 (2.9)	
Socioeconomic status					
1 (lowest)	2,227 (22.3)	1,887 (22.2)	303 (24.4)	37 (15.2)	0.05
2	2,075 (20.8)	1,762 (20.7)	270 (21.7)	43 (17.6)	
3	2,081 (20.8)	1,775 (20.9)	227 (18.3)	79 (32.4)	
4	1,878 (18.8)	1,616 (19.0)	213 (17.2)	49 (20.1)	
5 (highest)	1,732 (17.3)	1,467 (17.2)	229 (18.4)	36 (14.7)	
Stage[b]					
Metastatic	2,431 (27.7)	2,056 (26.9)	324 (34.8)	51 (23.3)	<0.01
Nonmetastatic	5,961 (67.8)	5,215 (68.3)	586 (62.9)	159 (73.0)	
Unknown	395 (4.5)	365 (4.8)	22 (2.4)	8 (3.7)	
Cancer diagnosis[c]					
Lymphoma	2,633 (26.4)	2,302 (27.1)	278 (22.4)	53 (21.7)	<0.01
Extracranial GCT	2,111 (21.1)	1,969 (23.2)	87 (7.0)	55 (22.5)	<0.01
Sarcoma	1,388 (13.9)	1,098 (12.9)	257 (20.7)	33 (13.5)	<0.01
Acute leukemia	1,206 (12.1)	870 (10.2)	310 (25.0)	26 (10.7)	<0.01
CNS malignancy	1,082 (10.8)	867 (10.2)	180 (14.5)	35 (14.3)	<0.01
Carcinoma	1,022 (10.2)	946 (11.1)	47 (3.8)	29 (11.9)	<0.01
Other	551 (5.5)	455 (5.3)	83 (6.7)	13 (5.3)	0.05

[a]Percentages represent distributions within provider subspecialty for all characteristics except total cohort number.
[b]Solid tumors only.
[c]See **Table 1** for specific cancers.

$P < 0.01$), and more often presented with metastases (34.8% vs. 26.9%; $P < 0.01$). A detailed summary of cancer diagnoses is shown in **Table 1**.

Patterns of care according to provider type

Distribution by age and diagnosis

Most patients (87.3%) received care from adult providers (excluding unknown physician type; $n = 244$, 2.4%), including 72.7% of those aged 15 to 19 years (**Fig. 1**). For every diagnosis, adult providers treated a greater absolute number of patients (**Table 2**). Adult providers cared for higher relative proportions of patients with lymphoma (27.1% for adult providers vs. 22.4% for pediatric providers) extracranial GCT (23.2% vs. 7.0%), and carcinoma (11.1% vs. 3.8%), whereas pediatric providers cared for higher relative proportions of patients with acute leukemia (25% for pediatric providers vs. 10.2% for adult providers), sarcoma (20.7% vs. 12.9%), and CNS malignancy (14.5% vs. 10.2%).

Within most major diagnostic categories, approximately 10% to 25% of these younger AYAs were treated by pediatric providers. This proportion was greater for certain cancers (**Table 1**). For example, pediatric providers treated more than one-fifth of these younger AYAs with ALL (43.8%), Ewing sarcoma (28.1%), osteosarcoma (27.5%), CNS GCT (25.0%), rhabdomyosarcoma (23.9%), and supratentorial primitive neuroectodermal tumor (PNET, 23.4%). For nearly all other diagnoses, adult providers treated more than 85% of the patients, including extracranial GCT (93.3%), carcinoma (92.6%), lymphoma (87.4%), and soft tissue sarcoma (85.1%). For most carcinomas, adult oncologists treated virtually all patients. Adult providers cared for 10 of 11 younger AYAs diagnosed with ganglioneuroblastoma and neuroblastoma, 4 of 6 with Wilms tumor, and 11 of 18 with other pediatric/embryonal cancers (**Table 1**).

Factors associated with provider type

In the first multivariable logistic regression model, where stage was excluded so that leukemia could be included, treatment by an adult provider was significantly associated with older age (OR, 1.93; 95% CI, 1.86–2.00; $P < 0.01$), female sex (OR, 1.18; 95% CI, 1.02–1.36, $P = 0.03$) and having extracranial GCT (OR, 2.26; 95% CI, 1.72–2.98; $P < 0.01$; **Table 3**). Conversely, treatment by a pediatric provider was significantly associated with non-white race (OR, 0.80; 95% CI, 0.69–0.94; $P < 0.01$) or with a diagnosis of leukemia (OR, 0.48; 95% CI, 0.39–0.59; $P < 0.01$), sarcoma (OR, 0.74; 95% CI, 0.60–0.92; $P < 0.01$) or CNS malignancy (OR, 0.76; 95% CI, 0.60–0.96; $P = 0.02$). Similar findings were obtained in the second model where leukemia was excluded in order to adjust for stage, but among these solid tumors, patients with nonmetastatic disease were more likely to see adult providers (OR, 1.93; 95% CI, 1.62–2.31; $P < 0.01$; **Table 3**).

Survival

The median follow-up time for the entire cohort was 91 months [interquartile range (IGR): 59–130]. Median follow-up times for patients treated by adult or pediatric providers were 92 months (IQR:

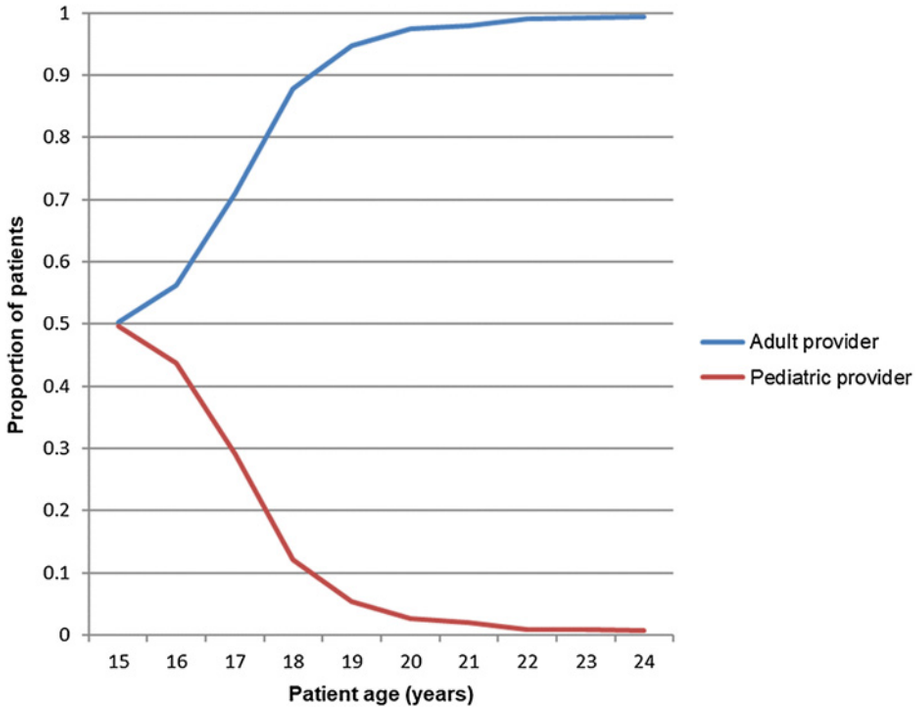

Figure 1.
Proportion of AYAs with cancer 15–24 years old by provider type and age at diagnosis. At age 15, AYAs were distributed evenly between pediatric (50.3%) and adult (49.7%) oncology providers; by age 19, over 90% of AYAs were linked to adult providers.

60–131), and 82 months (IQR: 38–119), respectively. Unadjusted 3-, 5-, and 8-year survival probabilities differed significantly by provider type for ALL and CNS malignancy (Supplementary Table S1). In multivariable models for the entire cohort excluding leukemia in order to adjust for stage, there was no survival difference by provider type [adjusted hazard ratio (aHR) adult vs. pediatric = 1.00; 95% CI, 0.86–1.18; $P = 0.98$; **Table 4**; **Fig. 2A**]. Similarly, no survival difference by provider type was noted for the broad categories of extracranial GCT,

Table 3. Multivariable analysis of factors associated with treatment of 9,993 AYAs 15 to 24 years old by an adult versus pediatric oncology provider.

	Excluding stage		Excluding diagnosis	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age	1.93 (1.86–2.00)	<0.01	1.88 (1.80–1.95)	<0.01
Sex				
Male	Referent		Referent	
Female	1.18 (1.02–1.36)	0.03	1.08 (0.92–1.27)	0.34
Race				
White	Referent		Referent	
Non-White	0.80 (0.69–0.94)	<0.01	0.77 (0.65–0.91)	<0.01
Socioeconomic status				
1 (lowest)	Referent		Referent	
2	0.98 (0.80–1.22)	0.87	1.03 (0.81–1.31)	0.83
3	1.19 (0.95–1.48)	0.13	1.20 (0.93–1.54)	0.16
4	1.10 (0.87–1.38)	0.44	1.12 (0.87–1.45)	0.38
5 (highest)	1.05 (0.83–1.32)	0.70	1.13 (0.87–1.47)	0.35
Diagnosis				
Lymphoma	Referent		—	—
Leukemia	0.48 (0.39–0.59)	<0.01		
Extracranial GCT	2.26 (1.72–2.98)	<0.01		
Sarcoma	0.74 (0.60–0.92)	<0.01		
CNS malignancy	0.76 (0.60–0.96)	0.02		
Other[a]	1.79 (1.41–2.27)	<0.01		
Stage				
Metastatic	—	—	Referent	
Nonmetastatic			1.93 (1.62–2.31)	<0.01
Unknown			2.80 (1.70–4.62)	<0.01

[a]Includes all carcinomas.

Table 4. Cox proportional hazard models for risk of death with treatment by an adult versus pediatric oncology provider among 9,993 AYAs 15 to 24 years old.

	aHR (95% CI)	*P*
Entire cohort[a]	1.00 (0.86–1.18)	0.98
Lymphoma	0.69 (0.48–0.99)	0.04
Hodgkin lymphoma	0.99 (0.53–1.83)	0.97
Non–Hodgkin lymphoma	0.61 (0.39–0.96)	0.03
Extracranial GCT	1.57 (0.82–3.00)	0.17
Sarcoma	1.01 (0.80–1.29)	0.91
Osteosarcoma	0.92 (0.60–1.41)	0.69
Ewing sarcoma	1.20 (0.74–1.94)	0.46
Rhabdomyosarcoma	2.22 (1.03–4.76)	0.04
Leukemia	0.94 (0.73–1.20)	0.60
ALL	1.19 (0.88–1.59)	0.25
AML	0.77 (0.51–1.15)	0.19
CNS malignancy	1.63 (1.12–2.37)	0.01
Carcinoma	0.66 (0.39–1.11)	0.12

[a]Excludes patients with a diagnosis of leukemia; see Methods.

sarcoma, acute leukemia, carcinoma, or for the specific diagnoses of Hodgkin lymphoma, osteosarcoma, Ewing sarcoma, ALL, or AML. Significantly higher survival was associated with pediatric providers for CNS malignancies (aHR, 1.63; 95% CI, 1.012–2.37; $P = 0.01$; **Fig. 2B**) and rhabdomyosarcoma (aHR, 2.22; 95% CI, 1.03–4.76; $P = 0.042$; **Fig. 2C**). Conversely, significantly higher survival was

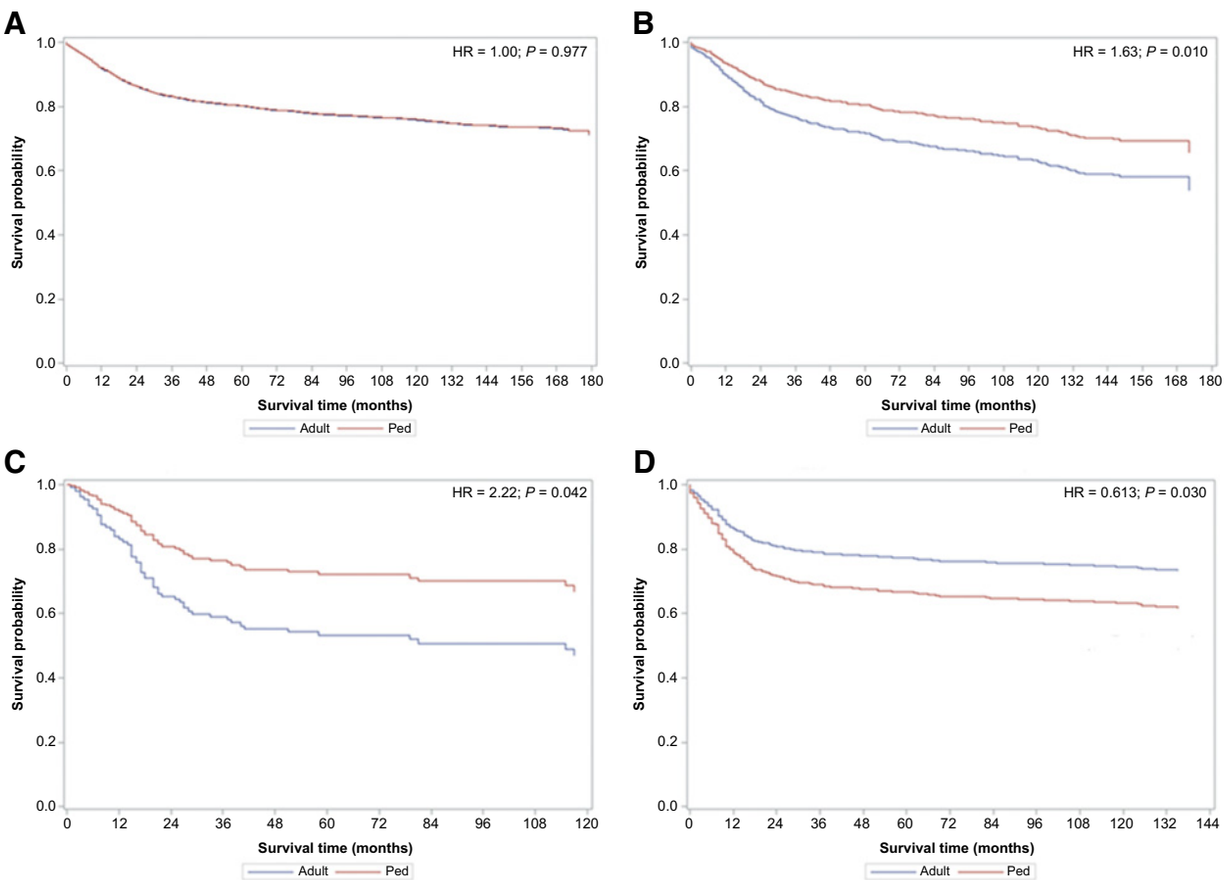

Figure 2.
Overall survival of AYAs with cancer 15–24 years old by provider type. **A,** Entire cohort excluding leukemia (932 pediatric, 7,637 adult). **B,** CNS malignancies (180 pediatric, 867 adult). **C,** Rhabdomyosarcoma (27 pediatric, 81 adult). **D,** Non–Hodgkin lymphoma (117 pediatric, 844 adult). Adapted from multivariable Cox regression analysis; see Methods. Ped, pediatric.

associated with adult providers for non–Hodgkin lymphoma (aHR, 0.61; 95% CI, 0.39–0.96; $P = 0.03$; **Fig. 2D**).

Discussion

In this study of younger AYAs, we utilized the large and socio-demographically diverse CCR to determine contemporary patterns of cancer care throughout California, as well as their impact on survival, on a scale and level of detail not previously described. Our study found that a majority of younger AYAs were treated by adult oncology providers, a finding not altogether unexpected but striking in its magnitude, even among teenagers 15 to 19 years old. Within every cancer type there was a markedly greater absolute number and proportion of younger AYAs cared for by adult providers. More surprising were patients cared for by adult providers even when diagnosed with "classic" pediatric cancers, including neuroblastoma, Wilms tumor, and pediatric embryonal neoplasms. Reasons for these overall patterns are unknown but could include the comparatively small number of pediatric oncologists available and travel distance to pediatric cancer centers (2, 7). This could result in referral biases of primary care providers or patient and family preferences to stay closer to home.

In adjusted multivariable models, we found that younger AYAs with extracranial GCTs were more likely to see adult providers whereas those with leukemia, sarcoma, or CNS malignancy were more likely to see pediatric providers. Reasons for this are speculative. Extracranial GCTs represent a large proportion of AYA cancers, and therefore most adult-focused providers have extensive experience with this diagnosis. In contrast, it is possible that medical oncologists in community-based settings feel less confident treating younger AYAs with acute leukemia and refer many to centers offering hematopoietic cell transplantation (HCT). Similarly, younger AYAs with sarcoma or CNS malignancies may require subspecialty surgical services resulting in referral to tertiary centers likely to offer pediatric providers. Having metastatic disease was independently associated with seeing pediatric providers, possibly because these AYAs are at higher risk for treatment failure and, again, may be referred to tertiary centers where pediatric oncologists are also based. Finally, patients of non-white race were more likely to see pediatric providers. Reasons for this are again speculative, but it may be that urban areas have higher proportions of non-white residents, (29) and most COG institutions are large tertiary care centers located in these same urban areas. Conversely, rural areas have a higher proportion of White residents (29). For rural residents it may often be a much longer distance to travel to the closest COG institution (and therefore pediatric provider) as opposed to the closest adult oncology practice.

The major finding of our study is that, for most cancers, treatment of AYAs aged 15 to 24 years by either adult or pediatric oncologists was not associated with a significant difference in observed survival. This must be interpreted thoughtfully, as discussed further below. An important exception to this finding was CNS malignancies, where higher age-adjusted survival was documented for treatment by pediatric providers. While it is conceivable that pediatric providers more commonly pursue aggressive resection, employ radiation, and utilize intensive chemotherapy in treating CNS malignancies among AYAs, this finding may be confounded by improved survival observed at high-volume tertiary care centers, the setting where most pediatric oncologists practice (30). The analysis was adjusted for diagnoses and there were not obvious differences in the proportions of higher-grade tumors by provider type to explain this survival pattern. Survival differences by provider type were also noted for younger AYAs with rhabdomyosarcoma and NHL, although their levels of significance were marginal and should be interpreted cautiously. Interestingly, we did not, in this population-based study, replicate the finding of others showing superior survival for AYAs with ALL treated by pediatric oncologists (7–15). This could be explained by the relatively long follow-up in our study where survival differences at earlier time points might no longer be significant, but another plausible explanation is that many younger AYAs treated by adult oncologists might have received HCT in first remission (15). It is important to emphasize that equivalent survival may not reflect equivalent quality of life when considering acute toxicity, late effects, psychosocial support, financial impact, and other qualitative outcomes that may differ between regimens.

An important concern is whether these results are generalizable to the remainder of the United States. Although exact comparisons are difficult, inferences can be drawn from state characteristics, cancer statistics, and oncology practice patterns. First, while California has a larger and more racially/ethnically diverse population with more foreign-born residents and multiple-language households than other states, it is mostly similar overall (31) and, like much of the United States, occupies a cross-section of urban, rural, and frontier areas (32). Second, the CCR is representative of this heterogeneity (33) and contributes about one third of all cases in the SEER registry (34), which is considered to be generalizable to non-SEER regions (35). Finally, in a recent oncology workforce report from the American Society of Clinical Oncology, although the distribution of medical and pediatric oncologists in relation to cancer incidence was somewhat variable across the United States, the Pacific division containing California was more similar than not to most other divisions (36). Collectively, these considerations seem to suggest the main conclusions of this study are unbiased by the data source and likely generalizable.

This study has several strengths and some limitations. Notable strengths are its large, socio-demographically diverse sample, extended median follow up of over 7 years, and focus on common AYA cancers treated by both medical and pediatric oncologists. Additionally, our study used a rigorous methodology for designating adult versus pediatric provider at the individual level. Most other studies examining this topic have categorically assigned patients at COG-affiliated centers as receiving pediatric care, but the reality is that most of those are tertiary care centers where many more adult oncologists practice and care for this population. Earlier studies also were either underpowered to detect smaller survival differences or were limited to just a few diagnoses, weaknesses offset by our study design. Our confidence regarding survival is greatest for cancers having a reasonably large and/or balanced number of AYAs in each provider category. This was the case for most cancer sites except the broad category of carcinoma, where 92.6% of patients were treated by adult oncologists; for certain carcinomas, fewer than 10 patients were linked with pediatric providers. Thus, prudence is needed in drawing conclusions about survival and implications for care of younger AYAs with carcinoma: the inability to detect a statistically significant survival difference does not necessarily equate to equivalent clinical expertise. Other study limitations are mostly inherent to registry-based research, including potential misclassification of provider type resulting from some patients transferring care to the other provider type, a possibility clinical experience suggests is uncommon. Although our study cohort was treated a decade ago, treatment paradigms for some cancers have only recently undergone substantial shifts in the era of targeted therapy and immunotherapy. The benefits of these newer

therapies are probably not yet reflected in any retrospective examination of registry data. Finally, the availability of only limited treatment data in the CCR and SEER registry prevents comparison of therapeutic regimens used by pediatric and adult providers, which could be valuable for explaining observed differences in survival and other health outcomes, including late effects.

What insights may be gained, and caveats applied, in interpreting this study? First, considering survival alone, our results suggest that current patterns of cancer referral and treatment have merit for most AYAs aged 15 to 24 years. Exceptions to this may include younger AYAs with CNS malignancies and possibly rhabdomyosarcoma, where management incorporating pediatric oncology expertise or regimens may be beneficial. For most forms of carcinoma, where our data show AYAs are rarely treated by pediatric providers, treatment by adult oncologists with vastly greater experience is more appropriate. Second, it must be acknowledged that endpoints other than survival should be considered in the care of AYAs, a population uniquely beset with formidable psychosocial and financial challenges. Referral to cancer treatment centers offering AYA programs may offer an advantage but for some patients must be balanced against added burdens of being far from home. Finally, similar survival regardless of provider type suggests that common ground exists for greater collaboration between the disciplines of pediatric and medical oncology, without which it is impossible to reach all AYAs. In cancers with similar outcomes, historical pediatric and adult treatment paradigms should be critically examined in terms of both survival and other health outcomes such as acute toxicity and late effects, including infertility, as well as financial and psychosocial impact. Toward that end, the NCI National Clinical Trials Network offers a framework for greater collaboration across the COG and adult-focused cooperative oncology groups for expanding AYA-specific clinical trials with multiple endpoints.

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Authors' Contributions

C.L. Collins: Conceptualization, data curation, investigation, methodology, writing–original draft, writing–review and editing. **J. Peng:** Software, formal analysis, validation, writing–review and editing. **S. Singh:** Software, formal analysis, validation, writing–review and editing. **A.S. Hamilton:** Conceptualization, supervision, writing–review and editing. **D.R. Freyer:** Conceptualization, supervision, methodology, writing–original draft, writing–review and editing.

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