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Estimating cancer treatment intensity from SEER cancer registry data: Methods and implications for population-based registry studies of pediatric cancers

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Abstract

Objective: The Intensity of Treatment Rating (ITR) Scale condenses treatment and clinical characteristics into a single measure to study treatment effects on downstream health outcomes across cancer types. This rating was originally developed for clinicians to determine from medical charts. However, large studies are often unable to access medical charts for all study participants. We developed and tested a method of estimating treatment intensity (TI) using cancer registry and patient self-reported data.

Methods: We estimated two versions of TI for a cohort of pediatric cancer survivors-one utilized information solely available from cancer registry variables (TI_R) and the other included registry and self-reported information (TI_S) from survey participants. In a subset of cases (n=135) for whom the gold standard TI (TI_C) was known, both TI_R and TI_S were compared to TI_C by calculating percent agreement and weighted Cohen's kappa, overall and within cancer subtypes.

Results: In comparison to TI_C, 71% of TI scores from both methods were in agreement ($k = 0.61$ TIR / 0.54 TI_S). Among subgroups, agreement ranged from lowest (46% TI_R/39% TI_S) for non-defined tumors (e.g. "Tumor-other"), to highest (94% TI_R/94% TI_S) for acute lymphoblastic leukemia (ALL).

Conclusions: We developed a methodology to estimate TI for pediatric cancer research when medical chart review is not possible. High reliability was observed for ALL, the most common pediatric cancer. Additional validation is needed among a larger sample of other cancer subgroups.

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The ability to estimate TI from cancer registry data would assist with monitoring effects of treatment during survivorship in registry-based epidemiological studies.

Keywords

Pediatric and adolescent cancer; treatment intensity; cancer registry; epidemiology

Introduction

Pediatric cancer treatments (e.g. surgery, radiation, chemotherapy), which vary in intensity and may affect different anatomic regions, commonly cause late effects, defined as adverse health outcomes attributed to cancer therapy that persist or emerge in the years following initial treatment. However, controlling for multiple single-treatment indicators may result in a loss of statistical power and/or may be insufficient to capture interactions between treatment modalities, dosage, and, in the case of regional therapies such as irradiation, the site of administration.

The Intensity of Treatment Rating Scale 3.0 (ITR-3) was developed to address the need for an objective, reliable and valid method of classifying pediatric cancer treatment protocols into similar intensity groups based on the likelihood of treatment-related long term effects. [1] By condensing many highly specific treatment protocols and disease characteristics into a single measure, the effect of treatment on health outcomes such as morbidity, late effects, healthcare utilization, and psychosocial wellbeing can be broadly compared across multiple cancer types and treatment regimens. The ITR-3 consists of 43 classification terms that describe which treatment intensity level to assign based on clinical and treatment characteristics corresponding to specific cancer sites and/or histologies (Appendix A). As originally developed, medical chart data are used to classify cases based on their cancer site, stage, and treatment into four levels of treatment intensity, where 1=least intensive (e.g. surgery only), 2=moderately intensive (e.g. chemo or radiation), 3=very intensive (e.g. 2 or more treatment modalities), and 4=most intensive (e.g. stem cell transplant). While there is potential for error in the abstracting of medical chart data, this method is regarded as the “gold standard” as it is based on objective patient and clinical characteristics obtained by clinicians directly from the medical chart, and was the method originally developed to determine the ITR.

Despite the empirical utility of treatment intensity groupings in pediatric cancer research, large population-based studies are often limited in the ability to access medical charts to obtain the information required to define treatment intensity. To address this limitation, we developed and tested method of estimating pediatric cancer treatment intensity using Surveillance, Epidemiology and End Results (SEER) cancer registry variables combined, for some cases, with patient self-reported data.

Methods

Study population

Cases for which methods of treatment intensity estimation were developed from a population based study of the health and healthcare utilization of pediatric cancer survivors called the Project Forward Cohort (PFC). Eligible cases were selected from the Los Angeles SEER registry and included any cancer diagnosed at age 19 or younger between 1996 and 2010 and who were between ages 18–29 at the time of study launch in 2015 (5–20 years post-diagnosis). There were 2,981 eligible cases identified and 1,248 participated by completing a survey. The survey included self-reported information relevant to treatment intensity classification including treatment modality (e.g. chemotherapy, radiation, etc.), and relapse. PFC participants did not differ from the population of eligible cancer survivors on age at diagnosis, time since diagnosis, current age, cancer type, or stage at diagnosis. However, females, non-Hispanic Whites, and those from higher SES neighborhoods were more likely to respond.

SEER cancer registry data was provided for each eligible sampled case and survey data was linked to the registry data for the subset who participated in the study. The cancer registry data includes clinical characteristics of the cancer and initial therapy received and is based information abstracted by hospital registrars approximately six months after diagnosis and is largely based on inpatient hospital records.

Overview of Methods

We developed two approaches for defining treatment intensity among participants in the PFC. Our first approach utilized only information solely available from cancer registry variables and was applied to the entire sample (n=2981), while the second approach included cancer registry variables in combination with self-reported information from the subset who completed the survey (n=1,248). We compared the results from both methods to the ITR determined by the ‘gold standard’ method of clinical review of medical charts using a subgroup of the survey respondents who had previously participated in a pilot version of the study (n=135). For this subgroup treatment intensity was determined by clinical review of medical charts as detailed in the ITR-3 guide.

SEER variable definitions used to match ITR-3 definition categories.

One key component of the ITR-3 score is the number of treatments a patient has received. We created dichotomous variables for receipt of each type of treatment The following were considered distinct treatment modalities, as determined by two pediatric oncologists, ST and DF: chemotherapy, surgery, radiation, transplant, and hormone therapy/immunotherapy/biotherapy (the latter considered as one treatment modality if any of these treatments received). After creating such dichotomous indicator variables for all treatment types, they were then summed to create an additional “number of treatment modalities” variable.

Specific cancer types were also included as ITR classifiers. Dichotomous indicators were created for the cancer types referenced specifically on the ITR-3, based either on the SEER site recode variable or histological groupings. Some cancer types used by the ITR3

guidelines are grouped by existing SEER site categories while others were based on histology codes. For example, brain tumors are a defined SEER site group, whereas germ cell tumors are not. Other customized histology groupings that we created included retinoblastoma, Langerhans cell histiocytosis, hepatoblastoma, B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, lymphoma, rhabdomyosarcoma, osteosarcoma, and neuroblastoma.

Clinical expertise required to determine priorities for use of registry variables

In addition to treatment modality, number of treatments, and site/histology codes, ITR-3 classification terms also reference stage at diagnosis for some cancers. However in some cases these classification terms are not sufficiently detailed to determine a single treatment intensity score due to overlapping clinical characteristics. In other words, some cases could 'qualify' for two different classification terms on the ITR-3 guide. This issue stems not from a limitation of data availability but rather a reliance in the ITR-3 guide on clinical expertise in determining the prevailing clinical characteristic(s) that indicate treatment intensity for some cases. Thus, prior to designing and applying our algorithm to estimate treatment intensity from registry data, for some cases we first needed to operationalize clinical input to determine which cancer site or histology would define each case in order to determine which classification to use. In the medical chart review methodology originally developed for the application of the ITR-3, these determinations were made by a nurse or oncologist using clinical knowledge. To address this issue, priorities were established (by ST and DF) to avoid conflicts when a single case could be placed into multiple treatment intensity classifications. For example, the ITR-3 indicates that osteosarcoma cases are assigned level 3 treatment intensity. It also specifies that non-brain tumors are assigned level 1 if their only treatment was surgery. However these categories are not mutually exclusive; both would apply to an osteosarcoma case who received only surgical treatment. Thus, clarification was needed to determine whether to assign treatment intensity based on the surgery-only classification or based on the osteosarcoma classification. These prioritizations are available in Appendix B.

Steps for Calculation of treatment intensity based solely on cancer registry variables

Step 1—The first step of our approach to estimating treatment intensity from cancer registry variables was to identify those cases which could be determined directly from routinely collected cancer registry variables that included sufficient detail for all years of diagnosis, including cancer site, histology, and treatment indicators (surgery, chemotherapy, radiation, and transplant). Some cases could be determined solely based on cancer site or histology while others required information on the total number and/or type of treatment modalities in order to assign treatment intensity.

Step 2a—For the remaining cases, we identified the ITR-3 classification terms that required information that was not routinely reported in the cancer registry, or was reported without complete detail. The first instance of limited data availability pertained to cancers for which stage at diagnosis is considered to determine treatment intensity, which included Wilms' tumor, hepatoblastoma, Hodgkin lymphoma, neuroblastoma, non-Hodgkin lymphoma, and rhabdomyosarcoma. The ITR-3 references stages such as 1, 2, 3, 4, IVB,

etc., depending on the cancer type. For cases diagnosed in or after 2004, stage at diagnosis is reported in the registry with this level of detail, but for cases diagnosed prior to 2004 only a cruder stage variable is available, which is limited to stages such as in situ, localized, regional, or remote (Appendix C). Of the cancer types in the PFC, 69.2% were diagnosed prior to 2004, so the crude stage variable was used to determine treatment intensity, with equivalencies between the crude and more detailed stages determined by ST.

Step 2b—Some leukemia diagnoses required additional information on risk level which is not a routinely coded cancer registry variable. Because leukemia is one of the most common pediatric cancers and is also the most common diagnosis in our cohort, we focused on obtaining additional information to better define these cases' risk level. Acute lymphoblastic leukemia cases diagnosed under age 1 or over age 10 are definitively high risk, so risk level for these cases could be assigned without the need for further treatment information, as age at diagnosis is available in the registry. However, cases diagnosed between ages 1 and 10 could be low, standard risk, or high risk depending on other factors. While there are no routinely collected cancer registry variables to capture this information, there are text variables that contain additional clinical or treatment notes made by cancer registrars. Thus, for acute lymphoblastic leukemia cases diagnosed between ages 1 and 10, this text data was used to identify information indicative of risk level.

To structure the review of this text data, ST developed a guide of terms indicative of high versus low/standard risk, based on treatment agent, cooperative group protocol number, or chromosomal characteristics. We systematically searched for these terms and matching results were assigned the corresponding risk level. For example, for acute lymphoblastic leukemia the word "doxorubicin" or its abbreviation were searched and all cases with this term were coded as low/standard risk, whereas the word "daunorubicin" indicated high risk. Only in limited cases were text fields reviewed individually (e.g. when a treatment agent was misspelled, it was checked to confirm the drug). If no information was available in the text variables to indicate risk level for these cases, they were assumed to be low/standard risk based on their age at diagnosis. For biphenotypic leukemia, treatment intensity is determined based on whether they were treated using a lymphoid-directed regimen or a myeloid-directed regimen. The treatment text data for these cases was also searched for keywords or protocol numbers that indicated treatment intensity level.

The last instance of limited data availability was relapsed disease, which is not captured by the registry. Thus, relapse could not be accounted for in our version of treatment intensity based solely on cancer registry variables.

Step 3—All cancer types that were not specifically referenced by name on the ITR-3 and were not classified in any of the previous steps were coded as either "Tumor, other," "Carcinoma NOS," or "Soft Tissue Sarcoma." Per the ITR-3, treatment intensity for these cancers was determined simply by the number of treatment modalities (e.g. 1 treatment modality = level 2, 2+ treatment modalities = level 3).

Calculation of treatment intensity based on cancer registry variables plus patient self-report

We followed the above steps with the addition of the self-reported relapse information which assisted with the treatment intensity calculation for 16 cases. We also developed rules to define treatment when cancer registry and self-reported information did not agree for the subset of patients who completed the survey. We erred on the side of greater inclusion, such that treatment was counted if reported in the registry even if the participant did not self-report it, and if a participant reported having received a treatment that was not reported in the registry, they were considered to have received that treatment.

Treatment intensity score validation

A subset of PFC participants (n=135) was used to determine the reliability of our estimated treatment intensity from both methods (cancer registry variables with and without use of patient self-report) with the treatment intensity obtained using the gold standard method of clinical review which had been previously determined because they took part in an earlier pilot study using medical chart abstraction[2] (this was considered the accurate treatment intensity). Weighted Cohen's Kappa was calculated overall and among cancer subgroups to assess reliability.

Results

Of the full PFC (n=2,981, eligible) and of survey participants (n=1,248 responders), 46.8% and 47.1%, respectively, were classified in Step 1 using SEER cancer registry variables that were routinely collected for all years of diagnosis in the PFC (1996–2010) (Table 1). 20.5% of the full sample and 21.2% of participants were classified in Step 2a, which required stage at diagnosis information. 25.1% of the full sample and 24.9% of participants were classified in Step 2b, which involved the use of text fields to gain additional information needed to determine treatment intensity that wasn't otherwise reported in standard SEER registry variables. 7.6% of the full sample and 6.3% of participants remained unclassified after the previous steps, and were then classified based on the number of treatment modalities received.

Validation results

Among all cases in the validation sample (n=135), 7.4%, 33.3%, 47.4%, and 11.9% had a treatment intensity level of 1, 2, 3, and 4, respectively, based on the gold standard method. Among the most common cancer subgroups in our sample, the percentages with estimated treatment intensity level 1–4 were as follows: acute lymphoblastic leukemia- 0.0, 26.5, 61.7, 11.8 brain tumors- 4.5, 50.0, 40.9, 4.6, other leukemias and lymphomas- 0.0, 31.8, 50.0, 18.2.

In the validation sample overall, 71% agreement was found between the gold standard chart-based treatment intensity and the estimated registry-only as well as registry + self-report versions, and the kappa coefficients were 0.61 and 0.54, respectively. Lowest agreement was found for non-ITR-defined tumors (e.g. "Tumor- other" or "Carcinoma NOS"), while highest agreement was found for acute lymphoblastic leukemia (Table 2). Overall, of the

treatment intensity scores estimated only from registry data that did not match the chart-defined treatment intensity score, the majority were underestimated, whereas of the scores estimated from registry and self-report data, while a greater proportion of the self-report scores were overestimated, due to higher levels of self-reported treatment.

Discussion

Efforts to leverage existing data are a priority in an era with increased access to large datasets, rapidly developing computing resources, and a focus on translational research. Tools that reduce the need for manual data collection have the potential to reduce research costs and extend the reach of existing data to support population-based research. Our method of estimating and validating treatment intensity for pediatric cancer survivors demonstrates promise in some areas, as well as opportunities for continued development and further validation in larger samples.

Given the limited sample size of most subgroups, definitive conclusions cannot be drawn for these cancer types. Rather, these subgroup analyses serve to identify cancer types for whom we were not able to reasonably accurately estimate treatment intensity, and thus require additional efforts to improve accuracy. The low reliability among the non-brain solid tumors (both ITR-defined and non-ITR-defined) may be attributed to several issues. First, these subgroups contain a wide range of tumor types. The subgroup analyses that were restricted to a single cancer (acute lymphoblastic leukemia, brain tumors) show high reliability ranging from 82–94%. It is likely that our treatment intensity estimation method's performance differs by tumor type, so a larger validation sample is needed to examine accuracy within more homogenous groups in order to identify the specific cancers for whom more targeted classification guidance is needed.

Other sources of inadequacy in the cancer registry data include the less specific stage at diagnosis variable used by the registry prior to 2004, as the majority of cases in our sample whose cancer type required stage information to classify treatment intensity were diagnosed before 2004 and thus did not have a fully detailed stage variable available. Additionally, the cancer registry's lack of follow up data contributes to lower reliability given that it does not capture treatment given after 6 months from diagnosis and does not capture relapse or subsequent treatments. Additionally, certain treatments such as ambulatory chemotherapy may not always be reported to the registry, which relies primarily on inpatient hospital records. These limitations would bias the registry-only version toward lower treatment intensity scores, which was evident in our analysis. While self-reported data has the advantage of capturing relapse, it is subject to recall issues which could bias the treatment intensity estimation toward either lower or higher scores. For example, participants diagnosed at younger ages may have never received complete information about their treatment as their care was mediated by caregivers, so self-reported treatment may be an underestimate. Alternatively, inaccurate recollection could also lead to over-reporting. Indeed, a larger proportion of self-report scores were overestimated relative to the true score in our sample. For example, some survivors may report as a relapse what was in fact a separate second cancer. A study from the Childhood Cancer Survivor Study found that nearly a third of pediatric cancer survivors were not able to confirm their correct diagnosis,

and 70% of those who received anthracyclines could not recall the treatment agent used, even when prompted with drug names.[3] Future development of this approach could examine whether self-reported information is more accurate and contributes to better estimation of treatment intensity among those more recently diagnosed and/or those diagnosed at older ages.

The very high accuracy of our estimated treatment intensity for acute lymphoblastic leukemia cases is encouraging, given that this is one of the most common pediatric cancers (accounting for approximately 25% of all pediatric cancer diagnoses[4]). Our method was able to capture important information to substantially improve risk level determination by using both standardized variables as well as registrar text variables. Creating a keyword guide to systematically search for indicators of risk level/treatment enabled us to take advantage of this unstructured data. While the need for a pediatric oncologist to construct this guide required additional time, this would not need to be re-created for new samples, lending itself to increased efficiency and broad application in future efforts. Creating such treatment keyword guides specific to other cancers may enable us to extend the use of the text fields to improve accuracy for those cancers for whom our method in its current form did not achieve high accuracy.

Further, it is important to acknowledge general caveats about use of the ITR. Treatment intensity as defined by the ITR-3 guide is useful for studying treatment effects across a range of diagnoses, but it must be reviewed and revised as new treatment regimens emerge. The guide must reflect current protocols to accurately group treatment/disease characteristics into common intensity levels. For example, as use of targeted bio-immunotherapies increases, the toxicity profile of regimens in which they are incorporated may decrease as they potentially replace conventional chemotherapeutic agents that have accounted for much of the toxicity of historical therapy. Thus, in order for the ITR to remain the valuable tool it is for estimating treatment intensity, it will continue to need periodic updating to reflect the evolution of cancer therapy. Similarly, investigators working with cancer registry data in this way must continue to utilize the appropriate version of the ITR guide that is valid for the treatment era of the subjects being studied.

An expansion of the ITR guide could also be developed explicitly for the purpose of estimating treatment intensity from registry data. This would entail the addition of classifiers to provide specific guidance for the histological subtypes not currently addressed specifically on the guide. In our approach based on the existing guide, treatment intensity for these cases was determined based on the broad criterion of number of treatment modalities received, and showed poor reliability against the score derived by the gold standard method. Further classification guidelines developed by clinicians for these cancers could contribute to more accurate coding.

To our knowledge, this use of cancer registry data to estimate treatment intensity has not been documented before. Treatment intensity has been used to study adverse health events, health behaviors (e.g. substance use, healthcare utilization, information seeking), mental health, quality of life, self-efficacy, cancer-related knowledge, and resilience among pediatric cancer survivors[5–16]. This method could be applied to cases from other regions

given that all US state cancer registries capture treatment information (in North American Association of Central Cancer Registries format), including those supported by the National Cancer Institute's SEER program as well as by the CDC's National Program of Cancer Registries. The creation of additional treatment intensity classification guidelines for specific cancers and validation in larger samples could increase the accuracy of this method and support expanded population research on the effects of treatment on the health and wellbeing of survivors of pediatric cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix B: Prioritizations for overlapping TI classification terms

Overlapping classification terms		Priority classifier selected	N(% of full sample[1])	N(% of survey participants[2])
Cancer site/type overlapping with histology				
Germ cell tumor	Brain tumor	Brain tumor	23(0.8)	14(0.01)
Neuroblastoma	Brain tumor	Brain tumor	10(0.3)	3(0.002)
JMML[3]	AML[4]	JMML	16 (0.5)	10(0.01)
APL[5]	AML	APL	31 (1.0)	14(0.01)
Cancer site/histology overlapping with treatment-only classifier[6]				
Osteosarcoma	Surgery only	Surgery only	2(0.1)	1(0.001)
Hodgkin lymphoma	Surgery only	Hodgkin lymphoma	8(0.3)	1(0.08)
Non-Hodgkin Lymphoma	Surgery only	Non-Hodgkin Lymphoma	2(0.1)	1(0.001)
Thyroid	Surgery only	Thyroid	25(0.8)	8(0.006)
Rhabdomyosarcoma	Surgery only	Rhabdomyosarcoma	4(0.1)	1(0.001)
Non-brain germ cell	Surgery only	Surgery only	12(0.004)	4(0.003)
Ewing Sarcoma	Surgery only	Ewing Sarcoma	0(0.0)	0(0.0)

[1] Number that had these overlapping classifiers in the full Project Forward Cohort, n=2,981

[2] Number that had these overlapping classifiers among Project Forward Cohort participants, n=1,248

[3] Juvenile myelomonocytic leukemia

[4] Acute myeloid leukemia

[5] Acute promyelocytic leukemia

[6] For example, one of the ITR-3 classifiers dictates that for all non-brain tumors, if surgery was the only treatment received then TI=1. However, there are multiple cancers that are listed elsewhere on the ITR-3 that automatically receive a higher TI score, regardless of treatment reported. For this reason, a determination needed to be made as to which classifier was priority.

Appendix C: Stage at diagnosis variables available in the Los Angeles SEER cancer registry, by year of diagnosis

SUMSTAGE (1988-current)	STAGE (1988–2015)	DERIVED_AJCC_STG_GRP (2004-current)	DERIVEDAJCC7STAGEGRP (2010-current)
0: In situ	00: 00 (In situ)	0:00	000: 0
1: Localized	10: I	01: 0a	010: 0a
2: Regional by direct extension	11: IA	02: 0is	020: 0is
3: Regional by lymph nodes	12: IB	10: I	100: I
4: Regional by direct extension and lymph nodes	13: IC	11: I, NOS	110: INOS
5: Regional, NOS	19: I, NOS	12: IA	120: IA
7: Remote	20: II	13: IA1	121: IANOS
8: Not abstracted	21: IIA	14: IA2	130: IA1
9: Unknown or not specified	22: IIB	15: IB	140: IA2
	23: IIC	16: IB1	150: IB
	29: II, NOS	17: IB2	151: IBNOS
	30: III	18: IC	160: IB1
	31: IIIA	19: IS	170: IB2
	32: IIIB	20: IEA	180: IC
	33: IIIC	21: IEB	190: IS
	39: III, NOS	22: IE	230: ISA(lymphoma only)
	40: IV	23: ISA	240: ISB(lymphoma only)
	41: IVA	24: ISB	200: IEA(lymphoma only)
	42: IVB	30: II	210: IEB(lymphoma only)
	43: IVC	31: II, NOS	220: IE(lymphoma only)
	49: IV, NOS	32: IIA	300: II
	90: Unstaged/ Occult	33: IIB	310: IINOS
	98: Not applicable	34: IIC	320: IIA
		35: IIEA	321: IIANOS
		36: IIEB	322: IIA1

SUMSTAGE (1988-current)	STAGE (1988–2015)	DERIVED_AJCC_STG_GRP (2004-current)	DERIVEDAJCC7STAGEGRP (2010-current)
		37: IIE	323: IIA2
		38: IISA	330: IIB
		39: IISB	340: IIC
		40: IIS	350: IIEA(lymphoma only)
		41: IIESA	360: IIEB(lymphoma only)
		42: IIESB	370: IIE(lymphoma only)
		43: IIES	380: IISA(lymphoma only)
		50: III	390: IISB(lymphoma only)
		51: III, NOS	400: IIS(lymphoma only)
		52: IIIA	410: IIESA(lymphoma only)
		53: IIIB	420: IIESB(lymphoma only)
		54: IIIC	430: IIES(lymphoma only)
		55: IIIEA	500: III
		56: IIIEB	510: IIINOS
		57: IIIE	520: IIIA
		58: IIISA	530: IIIB
		59: IIISB	540: IIIC
		60: IIIS	541: IIIC1
		61: IIIESA	542: IIIC2
		62: IIIESB	550: IIIEA(lymphoma only)
		63: IIIES	560: IIIEB(lymphoma only)
		70: IV	570: IIIE(lymphoma only)
		71: IV, NOS	580: IIISA(lymphoma only)
		72: IVA	590: IIISB(lymphoma only)
		73: IVB	600: IIIS(lymphoma only)
		74: IVC	610: IIIESA(lymphoma only)
		88: Not Applicable	620: IIIESB(lymphoma only)
		90: Occult	630: IIIES(lymphoma only)
		99: Unknown	700: IV
			710: IVNOS
			720: IVA
			721: IVA1
			722: IVA2
			730: IVB
			740: IVC
			888: NA
			900: OCCULT
			999: UNKOWN

References

1. Kazak AE, Hocking MC, Ittenbach RF, et al. (2012) A revision of the intensity of treatment rating scale: classifying the intensity of pediatric cancer treatment. Pediatric blood & cancer. 59: 96–9. [PubMed: 21858914]
2. Milam JE, Meeske K, Slaughter RI, et al. (2015) Cancer-related follow-up care among Hispanic and non-Hispanic childhood cancer survivors: The Project Forward study: Follow-Up Care Among Cancer Survivors. Cancer. 121: 605–13. [PubMed: 25345867]
3. Kadan-Lottick NS, Robison LL, Gurney JG, et al. (2002) Childhood cancer survivors' knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study. Jama 287: 1832–9. [PubMed: 11939869]
4. Wartenberg D, Groves FD, Adelman AS. (2008) Acute lymphoblastic leukemia: epidemiology and etiology. Acute leukemias: Springer pp. 77–93.
5. Milam J, Slaughter R, Meeske K, et al. (2016) Substance use among adolescent and young adult cancer survivors. Psycho - Oncology. 25: 1357. [PubMed: 26315824]
6. Miller KA, Wojcik KY, Ramirez CN, et al. (2017) Supporting long-term follow-up of young adult survivors of childhood cancer: Correlates of healthcare self-efficacy. Pediatric blood & cancer. 64: 358–63. [PubMed: 27567026]
7. Bitsko MJ, Cohen D, Dillon R, Harvey J, Krull K, Klosky JL. (2016) Psychosocial Late Effects in Pediatric Cancer Survivors: A Report From the Children's Oncology Group. Pediatric Blood & Cancer. 63: 337–43. [PubMed: 26488337]
8. Wettergren L, Kent EE, Mitchell SA, et al. (2017) Cancer negatively impacts on sexual function in adolescents and young adults: The AYA HOPE study. Psycho-Oncology. 26: 1632–9. [PubMed: 27240019]
9. Gardner MH, Mrug S, Schwebel DC, Phipps S, Whelan K, Madan-Swain A. (2017) Benefit Finding and Quality of Life in Caregivers of Childhood Cancer Survivors The Moderating Roles of Demographic and Psychosocial Factors. Cancer Nursing. 40: E28–E37.
10. Tobin J, Allem JP, Slaughter R, Unger JB, Hamilton AS, Milam JE. (2018) Posttraumatic growth among childhood cancer survivors: Associations with ethnicity, acculturation, and religious service attendance. Journal of Psychosocial Oncology. 36: 175–88. [PubMed: 28816639]
11. Germann JN, Leonard D, Heath CL, Stewart SM, Leavey PJ. (2018) Hope as a Predictor of Anxiety and Depressive Symptoms Following Pediatric Cancer Diagnosis. Journal of Pediatric Psychology. 43: 152–61. [PubMed: 29049751]
12. Ritt-Olson A, Miller K, Baezconde-Garbanati L, et al. (2018) Depressive Symptoms and Quality of Life Among Adolescent and Young Adult Cancer Survivors: Impact of Gender and Latino Culture. Journal of Adolescent and Young Adult Oncology. 7: 384–8. [PubMed: 29768076]
13. Sleight AG, Ramirez CN, Miller KA, Milam JE. (2018) Hispanic Orientation and Cancer-Related Knowledge in Childhood Cancer Survivors. Journal of Adolescent and Young Adult Oncology.
14. Cousineau MR, Kim SE, Hamilton AS, Miller KA, Milam J. (2019) Insurance Coverage, and Having a Regular Provider, and Utilization of Cancer Follow-up and Noncancer Health Care Among Childhood Cancer Survivors. Inquiry-the Journal of Health Care Organization Provision and Financing. 56.
15. Miller KA, Ramirez CN, Wojcik KY, et al. (2018) Prevalence and correlates of health information-seeking among Hispanic and non-Hispanic childhood cancer survivors. Supportive Care in Cancer. 26: 1305–13. [PubMed: 29124416]
16. Hsiao CC, Chiou SS, Hsu HT, Lin PC, Liao YM, Wu LM. (2018) Adverse health outcomes and health concerns among survivors of various childhood cancers: Perspectives from mothers. European Journal of Cancer Care. 27.

Table 1.

Number of cases classified at each step of our TI estimation algorithm

Algorithm step	Cancer sites/types included	N(% of full sample[1])	N(% of survey participants[2])
Step 1: Cases for whom TI determined with routinely collected cancer registry variables	Retinoblastoma, CML, LCH, brain, germ cell, thyroid, AML, APL, Ewings Sarcoma, JMML, nasopharyngeal carcinoma, osteosarcoma; any case that received transplant	1,395(46.8)	588(47.1)
Step 2a: Stage at diagnosis needed (crude stage used for cases diagnosed <2004)	Wilms' tumor, Hepatoblastoma, Hodgkin lymphoma, neuroblastoma, non-Hodgkin lymphoma, rhabdomyosarcoma	612(20.5)	265(21.2)
Step 2b: Treatment text fields searched for necessary information	Acute lymphoblastic leukemia, biphenotypic leukemia	748(25.1)	311(24.9)
Relapse: Unavailable in registry-only version	Various-self-reported relapse	0(0)	6(0.5)
Step 3: All remaining cases	Tumor, other, Carcinoma NOS, and Soft Tissue Sarcoma	226(7.6)	78(6.3)
	Total	**2,981 (100)**	**1,248 (100)**

Note: Numbers in each row exclude those already counted in previous rows

[1]Project Forward Cohort - all eligible cases, n=2,981. Estimated treatment intensity among the full cohort (participants and non-participants) includes registry data only

[2]Project Forward Cohort participants, n=1,248. Estimated treatment intensity among this sample of participants includes registry data as well as self-reported treatment information

Table 2.

Agreement between estimated TI and true TI among subsample of the Project Forward Cohort

	N(%) accurate R/S[1]	Weighted kappa R/S	p-value[2] R/S	N(%) of inaccurate cases that were under-estimated
Overall (n=135)	96(71)/96(71)	.61/.54	<.0001/<.0001	23(59)/17(44)
Acute lymphoblastic leukemia (n=34)	32(94)/32(94)	.84/.86	<.0001/<.0001	2(100)/1(50)
Other leukemia/lymphomas[3] (n=45)	28(62)/29(64)	.46/.50	.0003/<.0001	10(59)/9(56)
Brain (n=22)	18(82)/19(86)	.69/.81	.0003/<.0001	3(75)/3(100)
ITR-defined, non-brain solid tumors[4] (n=21)	12(57)/11(52)	.44/.27	.021/.037	5(56)/5(50)
Non-ITR-defined solid tumors[5] (n=13)	6(46)/5(39)	.57/.21	.05/.16	3(43)/2(25)

[1] R: Estimated TI using only registry data; S: Estimated TI using registry and self-report data (same cases used for each)

[2] H_0: The agreement between the estimate TI and the true TI is due to chance

[3] Acute myeloid leukemia, acute promyelocytic leukemia, juvenile monomyelocytic leukemia, biphenotypic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic myeloid leukemia

[4] Germ cell tumors, Wilms tumor, rhabdomyosarcoma, thyroid cancer, Ewing's sarcoma, nasopharyngeal carcinoma, osteosarcoma, neuroblastoma

[5] Cancers that were not named specifically in the ITR-3 were captured as either 'Tumor, other,' 'Carcinoma NOS,' or 'Soft tissue sarcoma.' After all other cancers were classified, these remaining cases with unassigned TI were classified just by the number of treatment modalities, per the ITR-3 guide.