Oct 6, 2022

Long-term Morbidity and Mortality of Childhood, Adolescent and Young Adult Cancers

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SCOR The Art & Science of Risk | Life

Childhood Cancer and Cancer Survivorship

AGENDA

1. Epidemiology of Cancer Survivorship
2. Childhood Cancers
3. Hematopoietic Cell Transplant (HCT) Review
4. Childhood HCT
5. Adult HCT
6. Review
7. Questions

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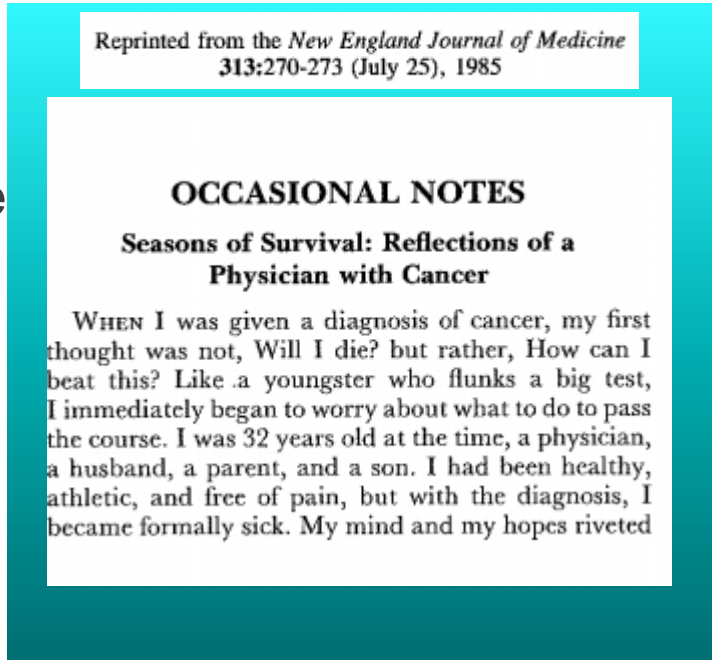
Cancer Survivor

- Definition acknowledged by
  - Institute of Medicine
  - Centers for Disease Control and Prevention (CDC)
  - American Society for Clinical Oncology
  - National Cancer Institute's Office of Cancer Survivorship

- National Coalition for Cancer Survivorship
  - Pre-1986 → Cancer victim
  - Dr. Fitzhugh Mullan

    cancer survivor
  - From the time of diagnosis → end of life

  - PAST, CANCER SURVIVOR = FREE OF CANCER DISEASE FOR 5 YEARS



Reprinted from the *New England Journal of Medicine*
313:270-273 (July 25), 1985

OCCASIONAL NOTES

Seasons of Survival: Reflections of a Physician with Cancer

WHEN I was given a diagnosis of cancer, my first thought was not, Will I die? but rather, How can I beat this? Like a youngster who flunks a big test, I immediately began to worry about what to do to pass the course. I was 32 years old at the time, a physician, a husband, a parent, and a son. I had been healthy, athletic, and free of pain, but with the diagnosis, I became formally sick. My mind and my hopes riveted

Cancer Survivorship: Global Surveillance

Five-Year Survival Rates for Patients Diagnosed with Five Common Cancers in Seven Countries 2010-2014

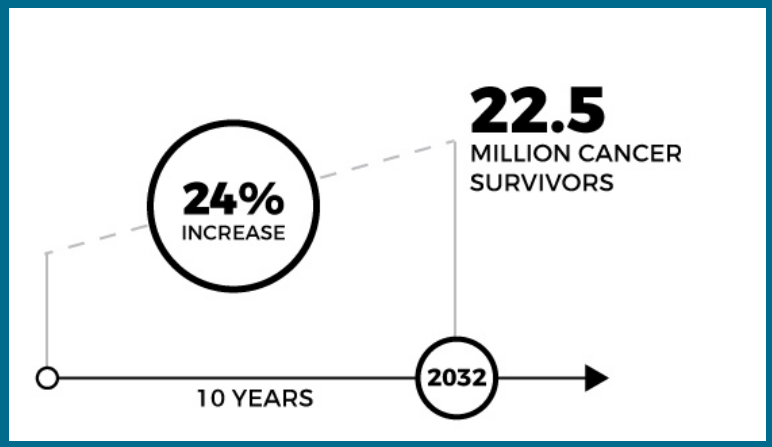
Country	Female Breast	Colon	Lung	Prostate	Childhood ALL
Australia	89.5	70.7	19.4	94.5	90.7
Canada	88.2	67.0	20.6	93.6	92.6
China	83.2	57.6	19.8	69.2	57.7
New Zealand	87.6	64.0	15.3	90.3	91.4
Japan	89.4	67.8	32.9	93.0	87.6
United Kingdom	85.6	60.0	13.3	88.7	92.2
United States	90.2	64.9	21.2	97.4	89.5

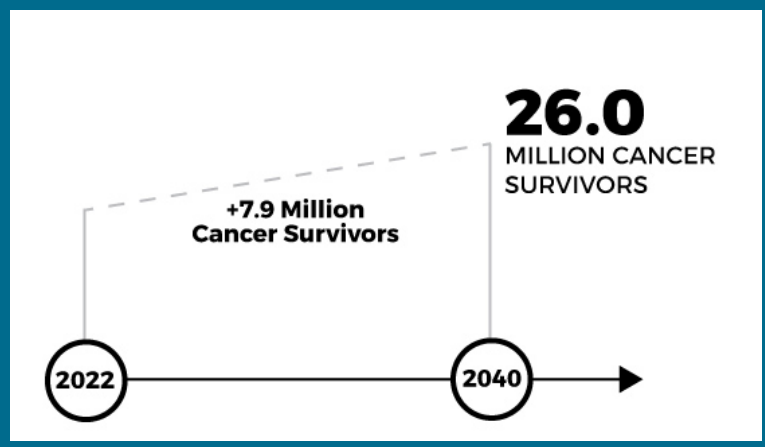
1) Allemani, Claudia, et al. "Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries." *The Lancet* 391.10125 (2018): 1023-1075.

Cancer Survivorship

NATIONAL CANCER INSTITUTE
Division of Cancer Control & Population Sciences

January 2022
5.4% of the US population





1) https://cancercontrol.cancer.gov/ocs/statistics/index.html

Cancer Survivorship

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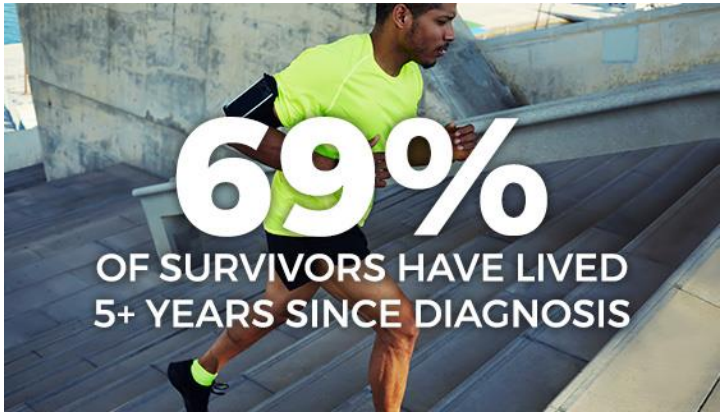
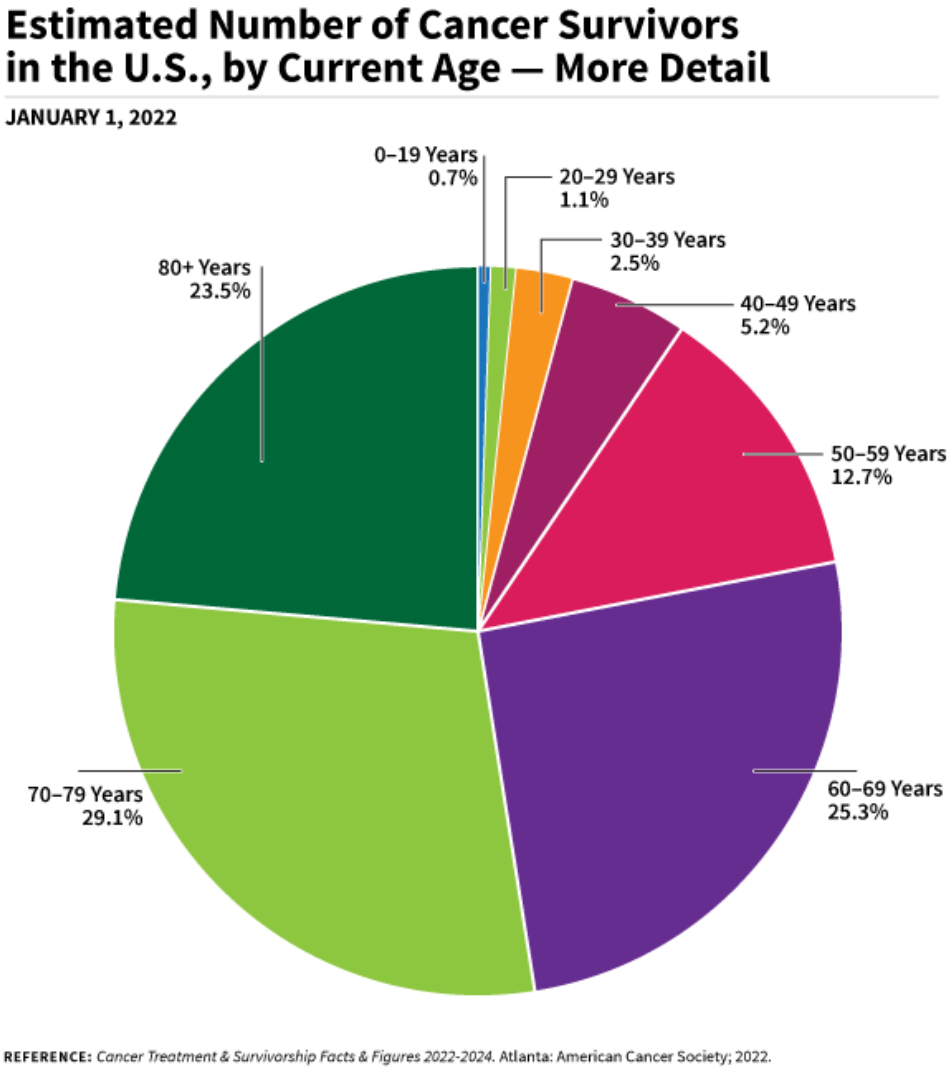


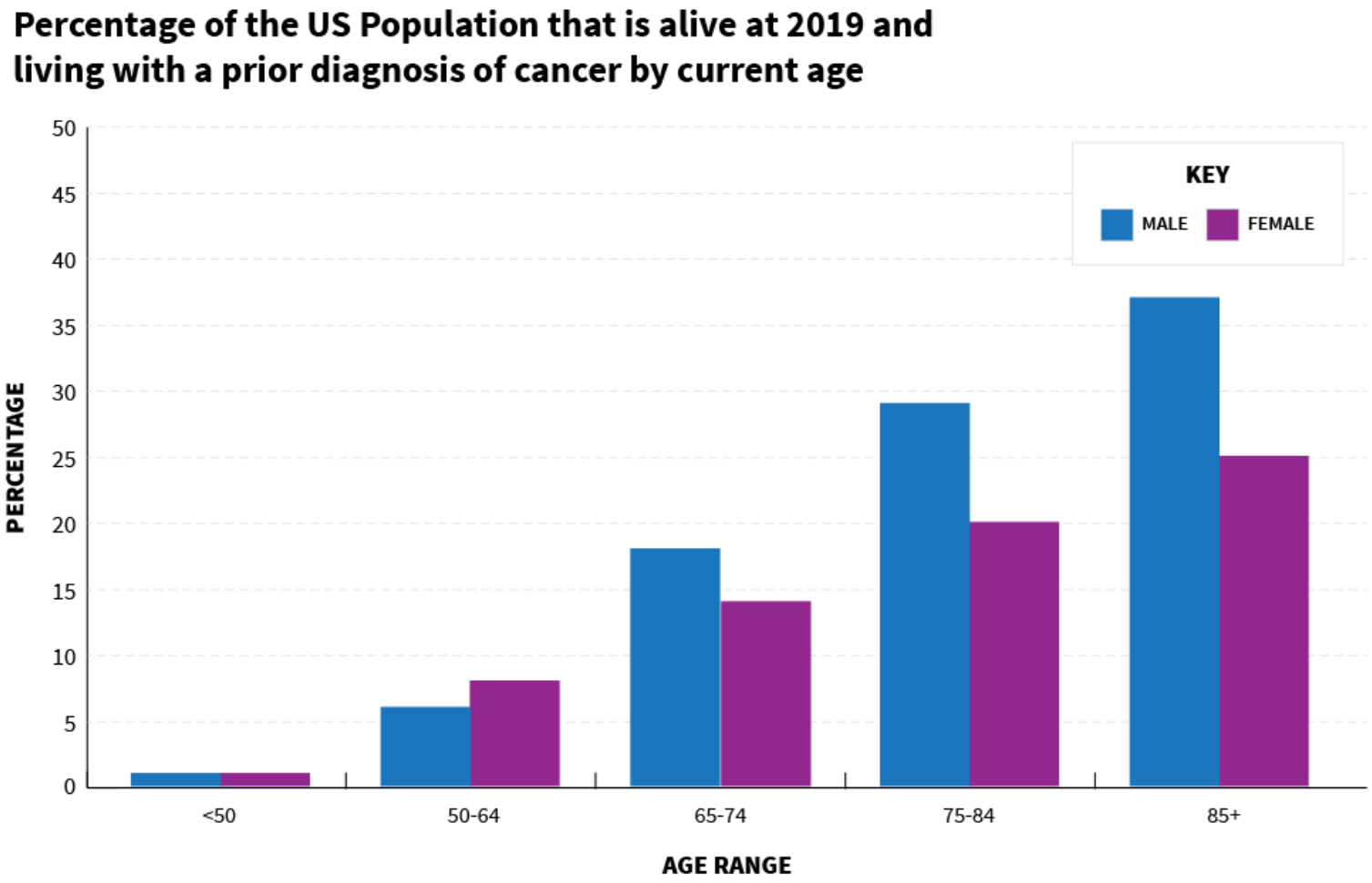
1) https://cancercontrol.cancer.gov/ocs/statistics/index.html

Cancer Survivorship



1) https://cancercontrol.cancer.gov/ocs/statistics/index.html

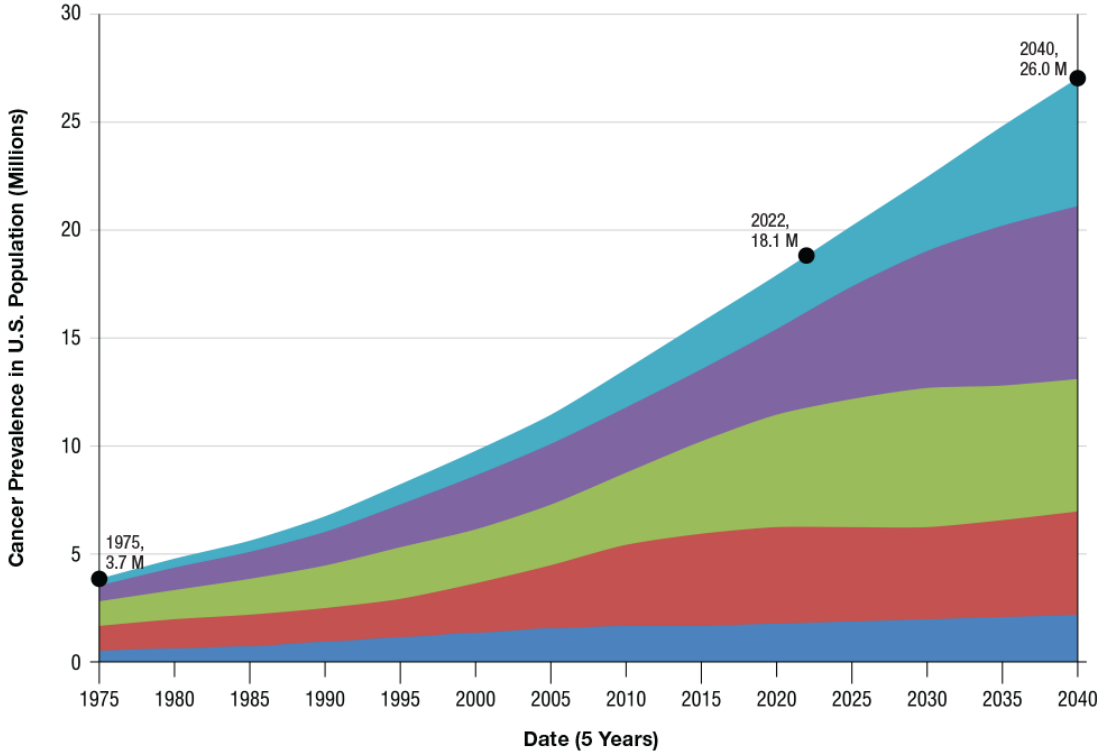
Cancer Survivorship



1) Cancer.gov accessed 11-7-2019

Cancer Survivorship

Cancer Prevalence and Projections in U.S. Population from 1975–2040



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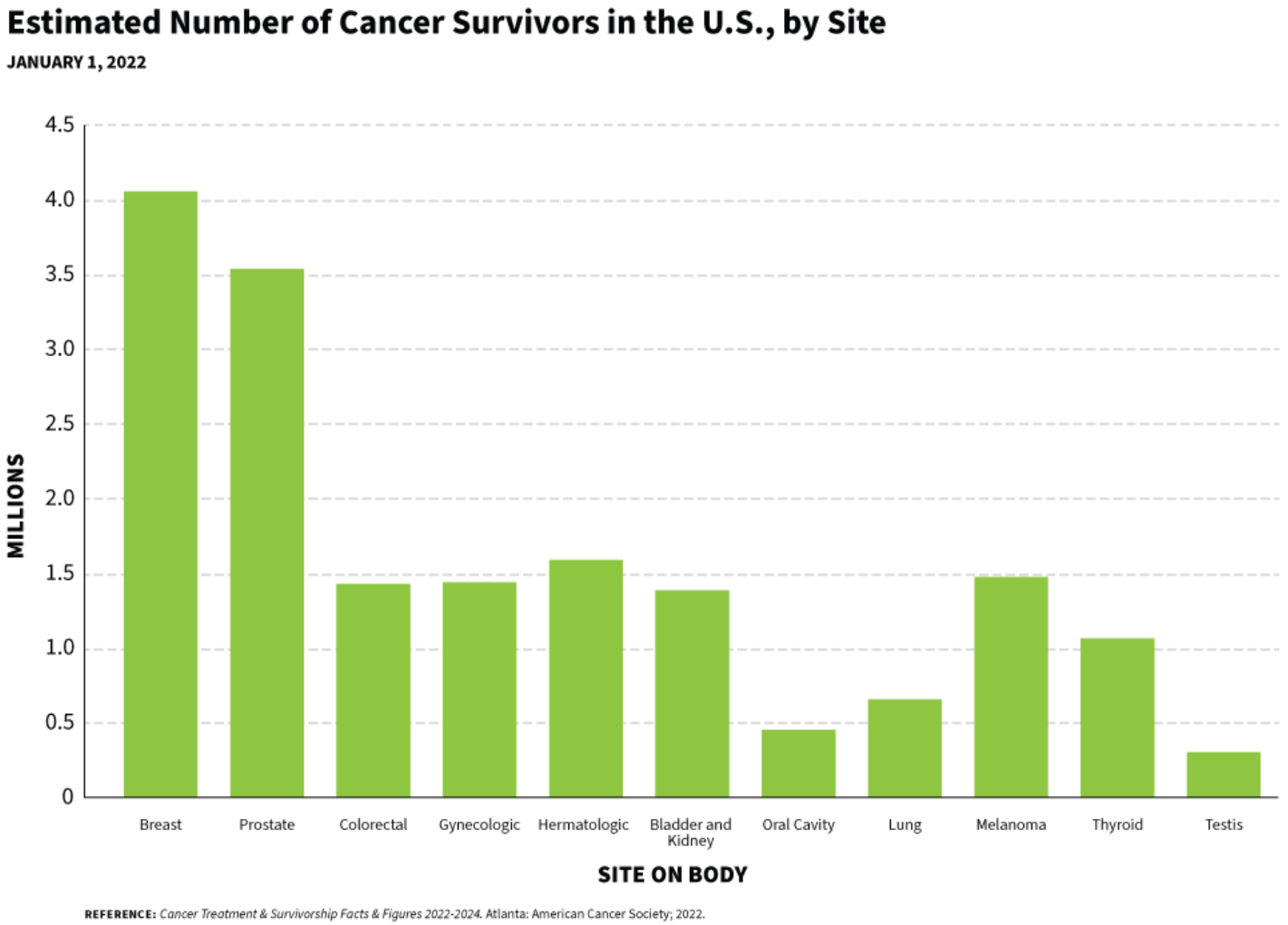
Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1029-36.

Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J and Siegel RL. Cancer Treatment and Survivorship Statistics. CA A Cancer J Clin. 2022.

Cancer Survivorship



1) https://cancercontrol.cancer.gov/ocs/statistics

Cancer Survivorship

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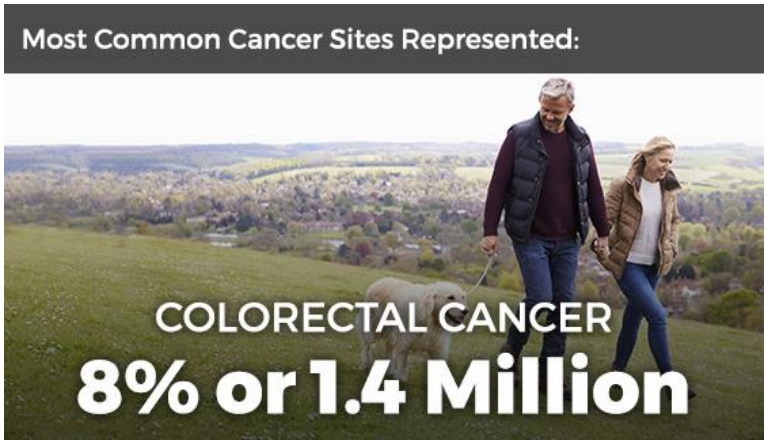

1) https://cancercontrol.cancer.gov/ocs/statistics/index.html

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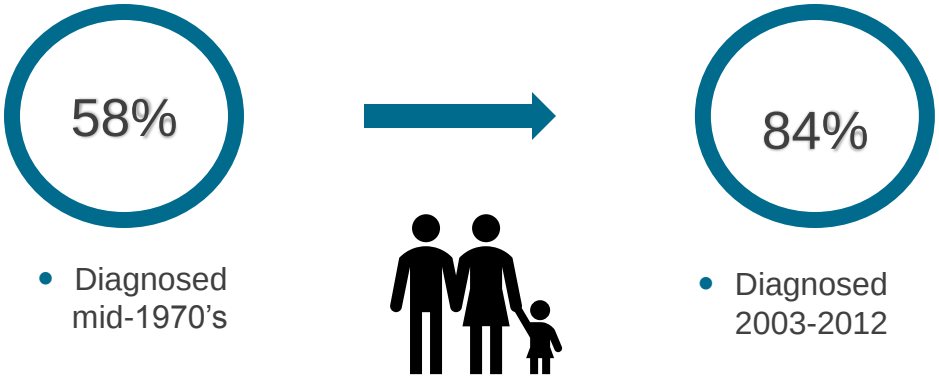
Childhood Cancer in US

5-year survival for childhood cancer continues to improve



1) https://www.cancer.org/cancer/cancer-in-children/key-statistics.html

Childhood Cancer?

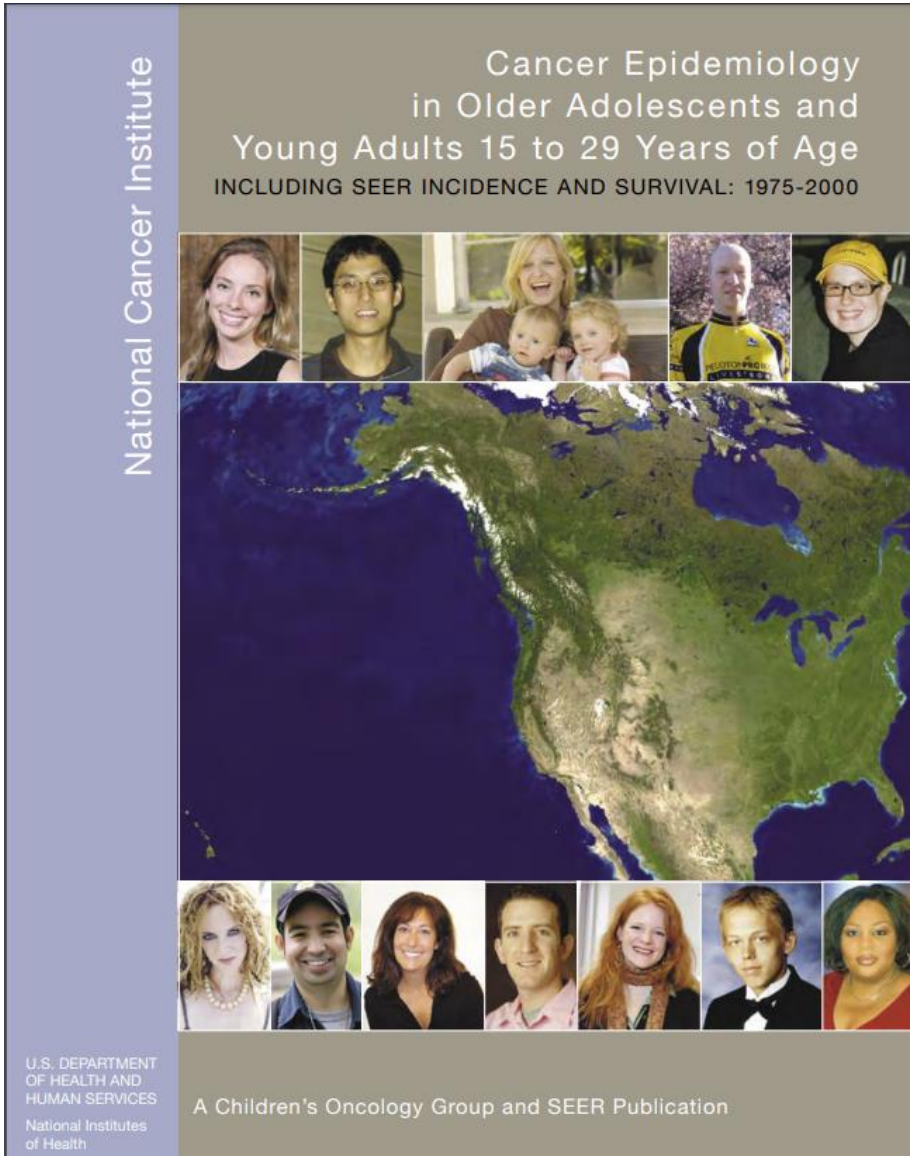
What is CHILDHOOD CANCER?

- 0-14 years?
- 0-19 years?
- 0-29 years?
- 0-39 years?

What is ADOLESCENT AND YOUNG ADULT CANCER?

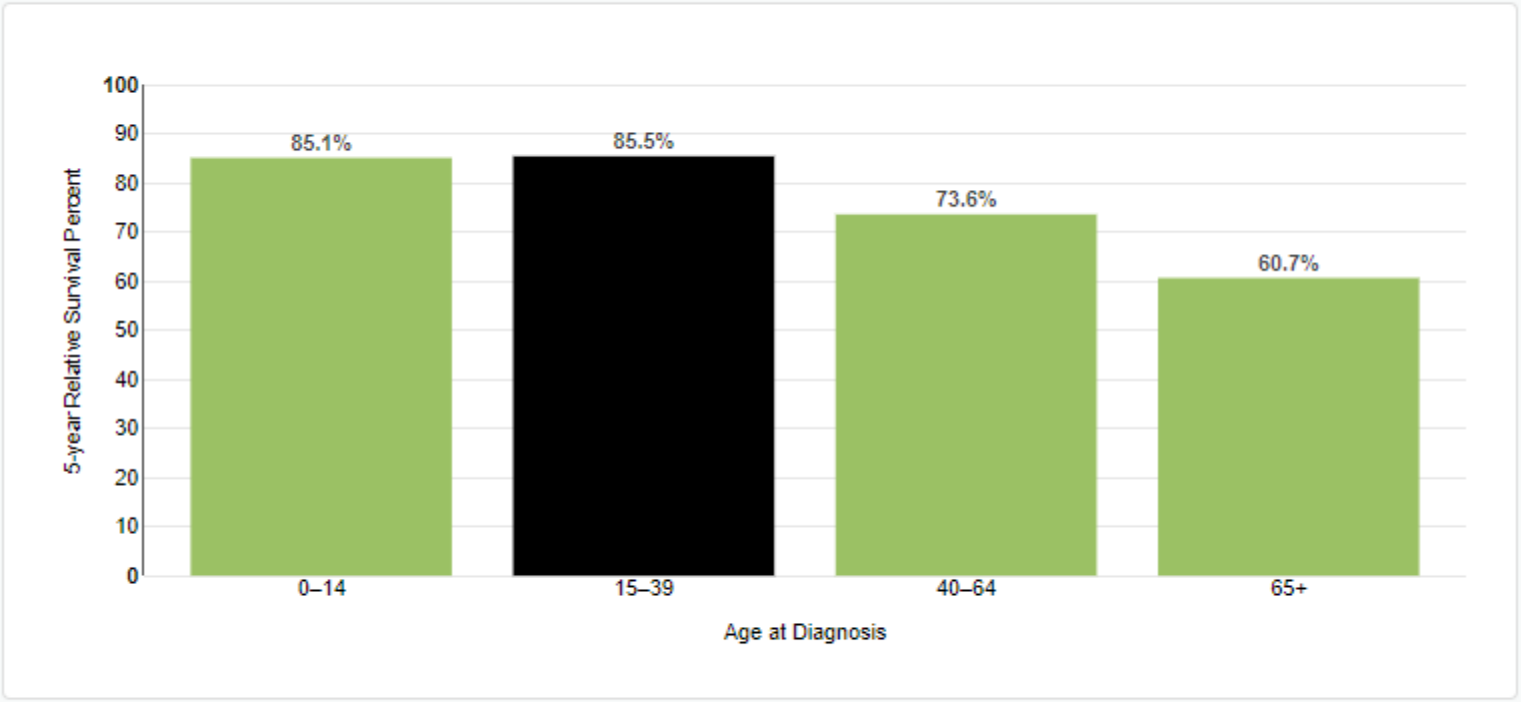
- 13-31 years?
- 15-25 years?
- 15-29 years?
- 15-39 years?

AYA Cancer


National Cancer Institute
Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age
INCLUDING SEER INCIDENCE AND SURVIVAL: 1975-2000
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
A Children's Oncology Group and SEER Publication

AYA Cancer

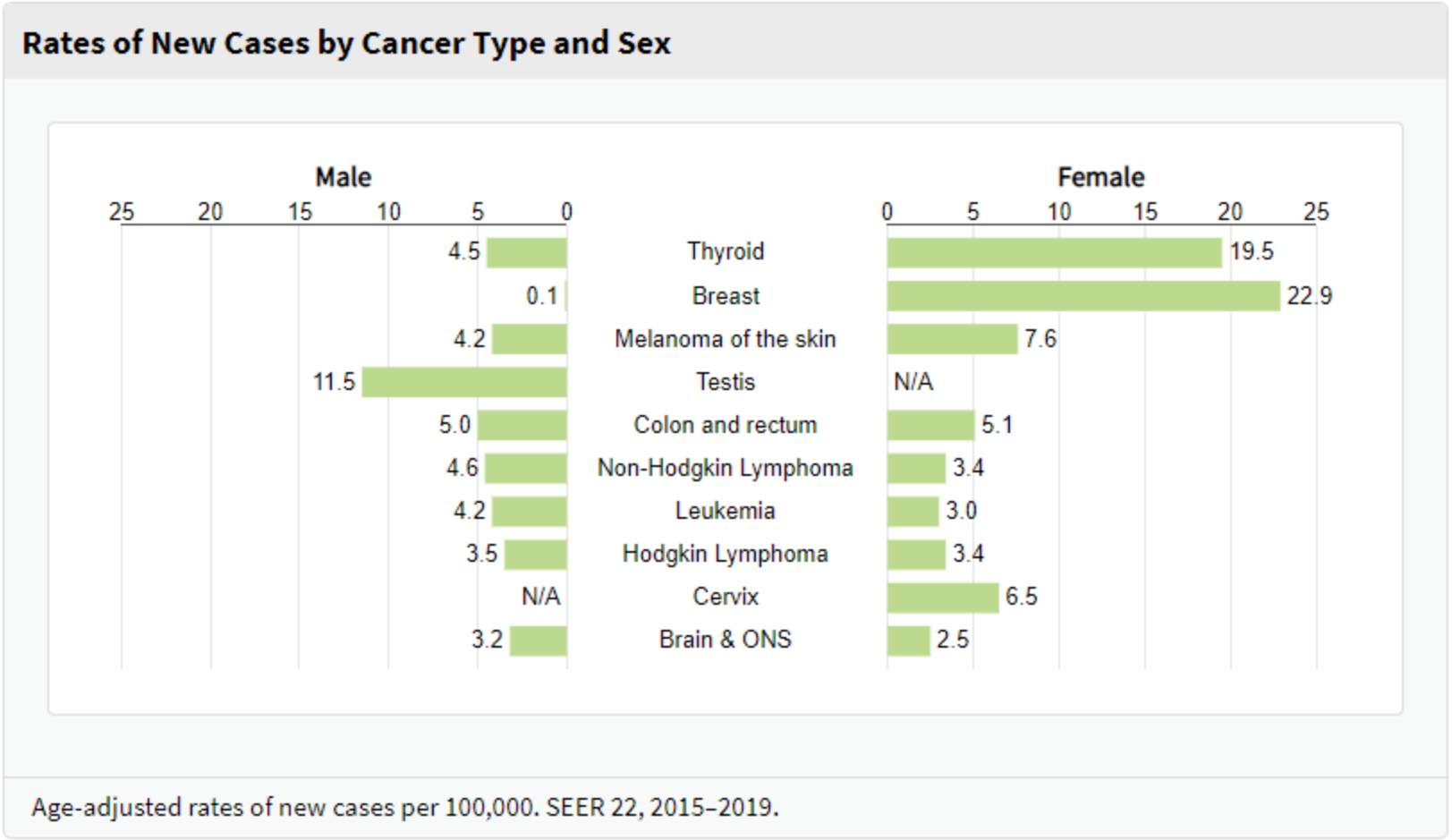
How Does Cancer Survival Among AYAs Compare to Cancer Survival at Other Ages?



SEER 17 2012–2018

1) https://seer.cancer.gov/statfacts/html/aya.html

US AYA Cancer



1) https://seer.cancer.gov/statfacts/html/aya.html

US Cancer AYA

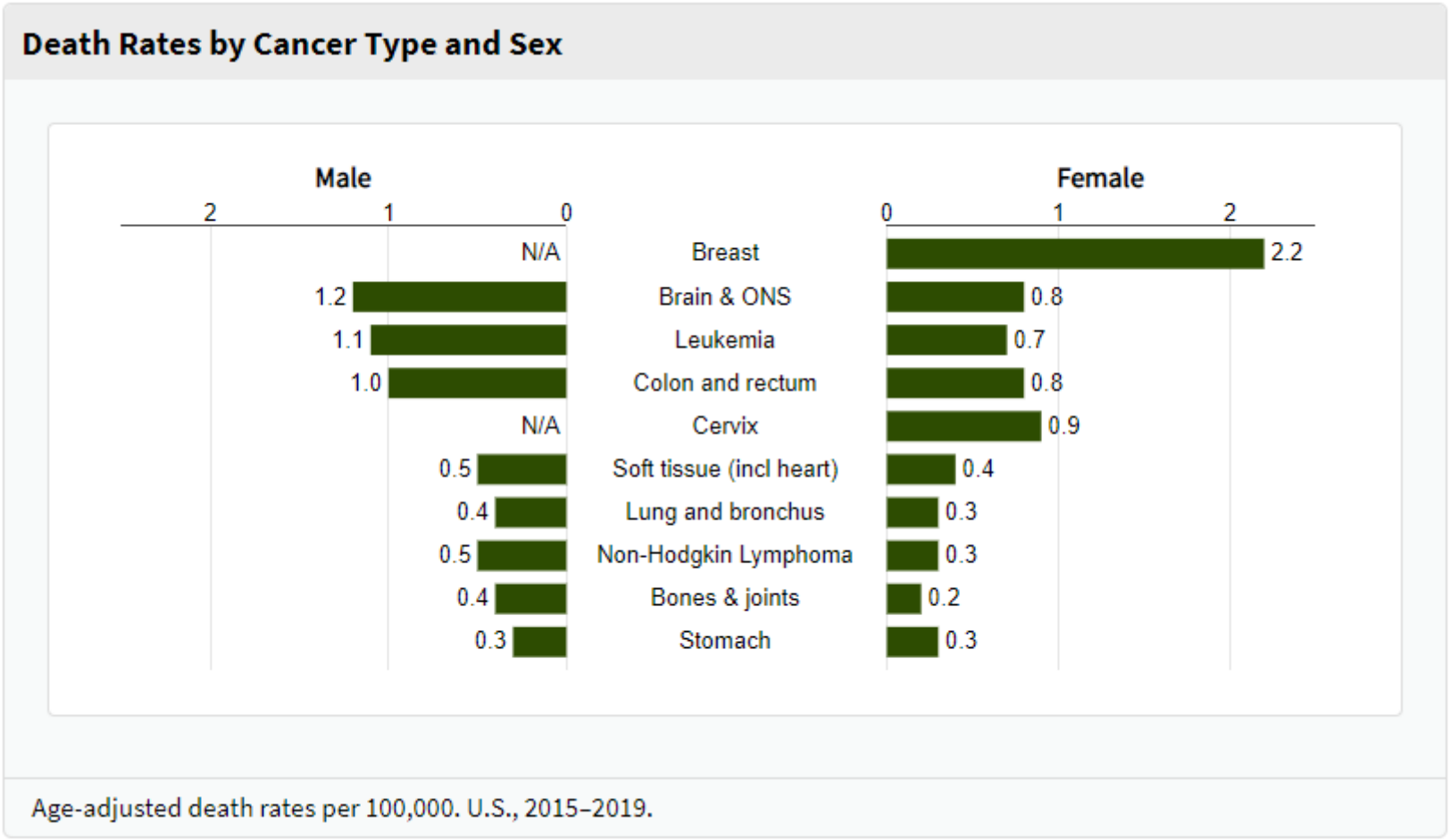
5-Year
Relative Survival

85.5%

Based on data from SEER 17 2012–2018. Gray figures represent AYAs who have died from cancer within 5 years of diagnosis. Green figures represent those who have survived 5 years or more.

1) https://seer.cancer.gov/statfacts/html/aya.html

US Cancer AYA



1) https://seer.cancer.gov/statfacts/html/aya.html

US Cancer AYA

Figure S2. Leading Sites of New Cancer Cases in AYAs, Both Sexes Combined – 2020 Estimates

Estimated New Cases

Ages 15-19		Ages 20-29		Ages 30-39	
Thyroid	800	Thyroid	4,600	Breast (female)	11,100
Hodgkin lymphoma	800	Testicular germ cell tumors	3,000	Thyroid	9,000
Brain & ONS	500	Melanoma of the skin	2,200	Melanoma of the skin	5,500
Non-Hodgkin lymphoma	500	Hodgkin lymphoma	2,000	Colon & rectum	4,100
Testicular germ cell tumors	400	Breast (female)	1,500	Testicular germ cell tumors	3,100
Acute lymphoid leukemia	400	Non-Hodgkin lymphoma	1,400	Uterine cervix	3,000
Bone tumors	400	Colon & rectum	1,300	Non-Hodgkin lymphoma	2,700
Soft tissue sarcomas	400	Brain & ONS	1,200	Kidney	2,400
Melanoma of the skin	200	Soft tissue sarcomas	1,000	Uterine corpus	2,000
Acute myeloid leukemia	200	Uterine cervix	800	Brain & ONS	1,800

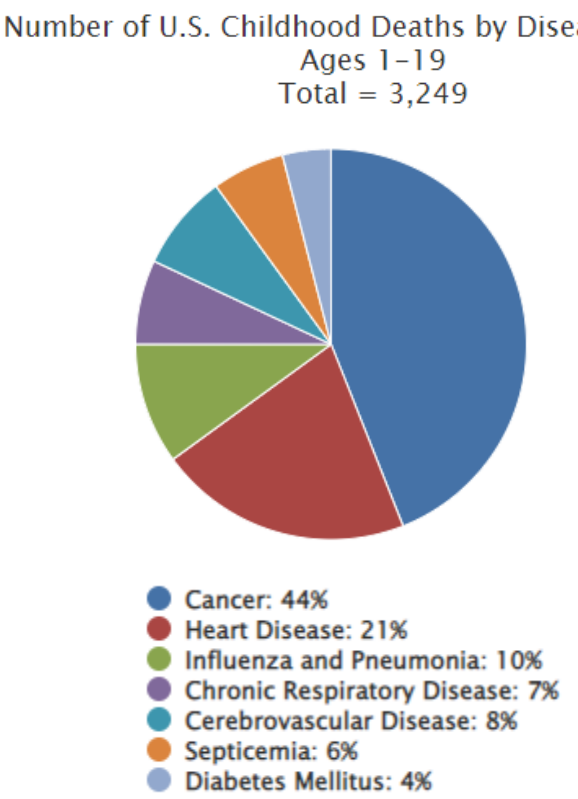
ONS = other nervous system. Estimates are rounded to the nearest 100 and exclude basal cell and squamous cell skin cancers, benign and borderline brain, and in situ carcinoma of any kind. Ranking is based on modeled progress and may differ from the most recent observed data.

©2020, American Cancer Society, Inc., Surveillance Research

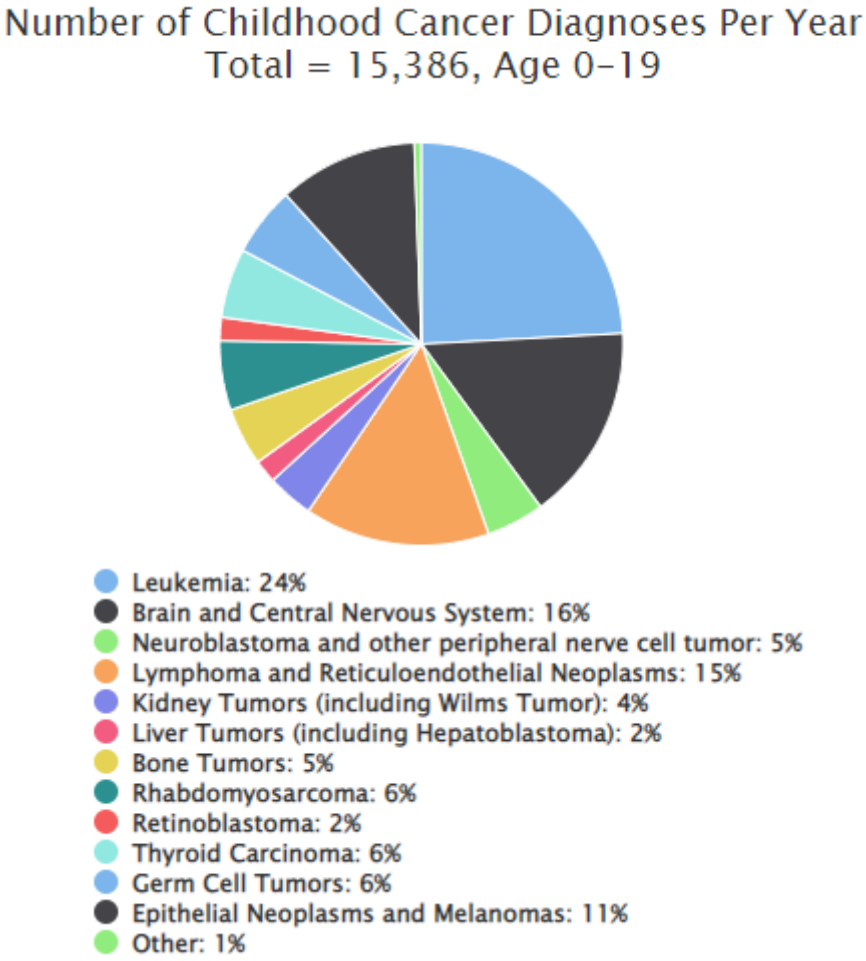
1) https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html

Childhood Cancer

Cancer diagnosis and cancer deaths in children US



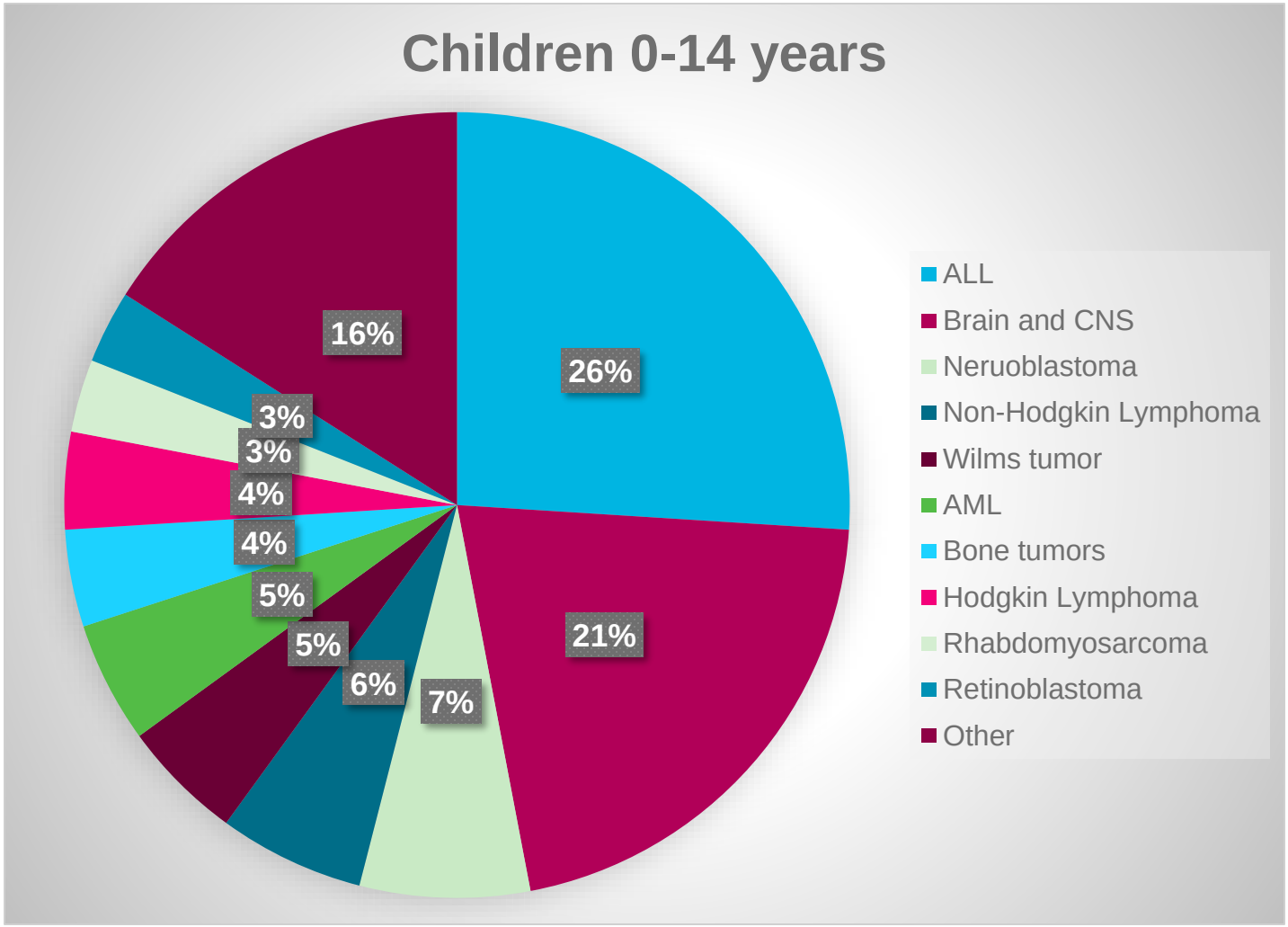
- Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality 1999-2020 on CDC WONDER Online Database, released in 2021. Data are from the Multiple Cause of Death Files, 1999-2020, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at wonder.cdc.gov/ucd-icd10.html on Jul 15, 2022 9:59:31 AM.



- :Source: NCCR*Explorer: An interactive website for NCCR cancer statistics [Internet]. National Cancer Institute. [Cited 2021 October 30]. Available from NCCRExplorer.ccdi.cancer.gov..

1) https://curesearch.org/

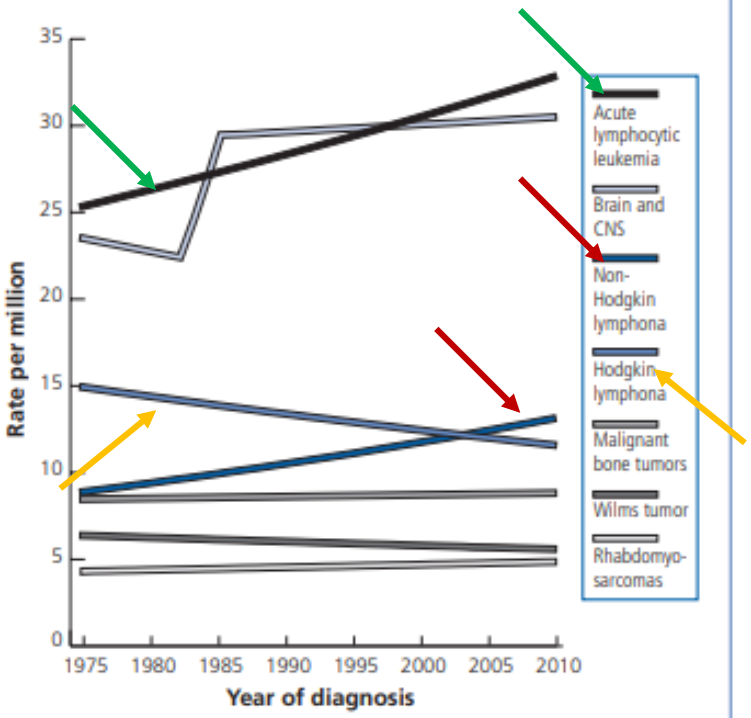
Childhood Cancer Estimated Cases US 2014



1) https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2014.html

Trends

Figure 2. Trends in Pediatric Cancer Incidence Rates by Site, Ages 0-19, 1975-2010



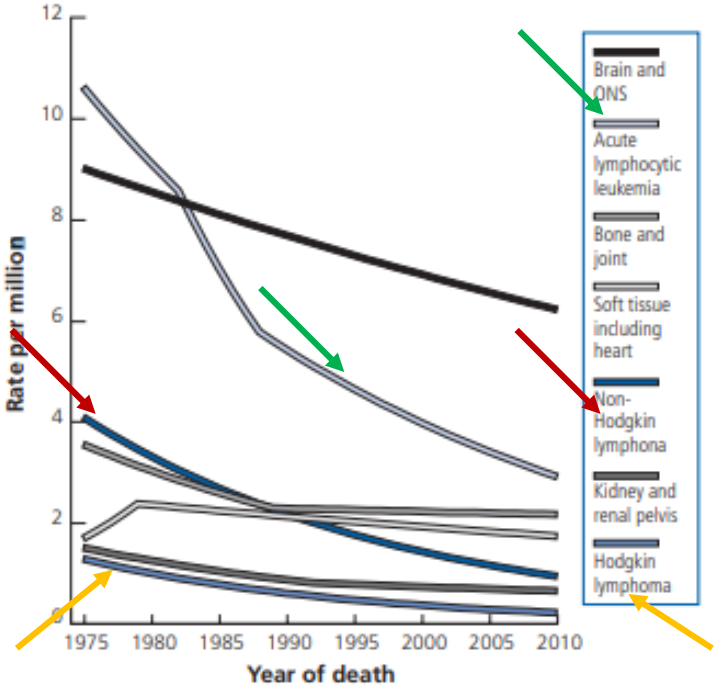
CNS = Central nervous system.

Note: lines represent Joinpoint fitted trends. Benign and borderline brain tumors are not included. Malignant bone tumors include osteosarcoma and Ewing sarcoma. Average annual percent change (APC) for cancers with significant trends during most recent period: ALL (0.7), NHL (1.1), and Hodgkin lymphoma (-0.7).

Source: Surveillance, Epidemiology, and End Results (SEER) Program, 9 SEER Registries, National Cancer Institute.

American Cancer Society, Surveillance Research, 2014

Figure 3. Trends in Pediatric Cancer Mortality Rates by Site, Ages 0-19, 1975-2010



ONS = Other nervous system.

Note: Lines are fitted trends based on Joinpoint analyses.

Average annual percent change (APC) for cancers with significant trends during most recent period: ALL (-3.1 during 1988-2010), brain (-1.1 during 1975-2010), NHL (-4.1 during 1975-2010), soft tissue (-1.0 during 1979-2010), kidney (-1.2 during 1992-2010), HL (-4.9 during 1975-2010).

Source: National Center for Health Statistics, Centers for Disease Control and Preventaion.

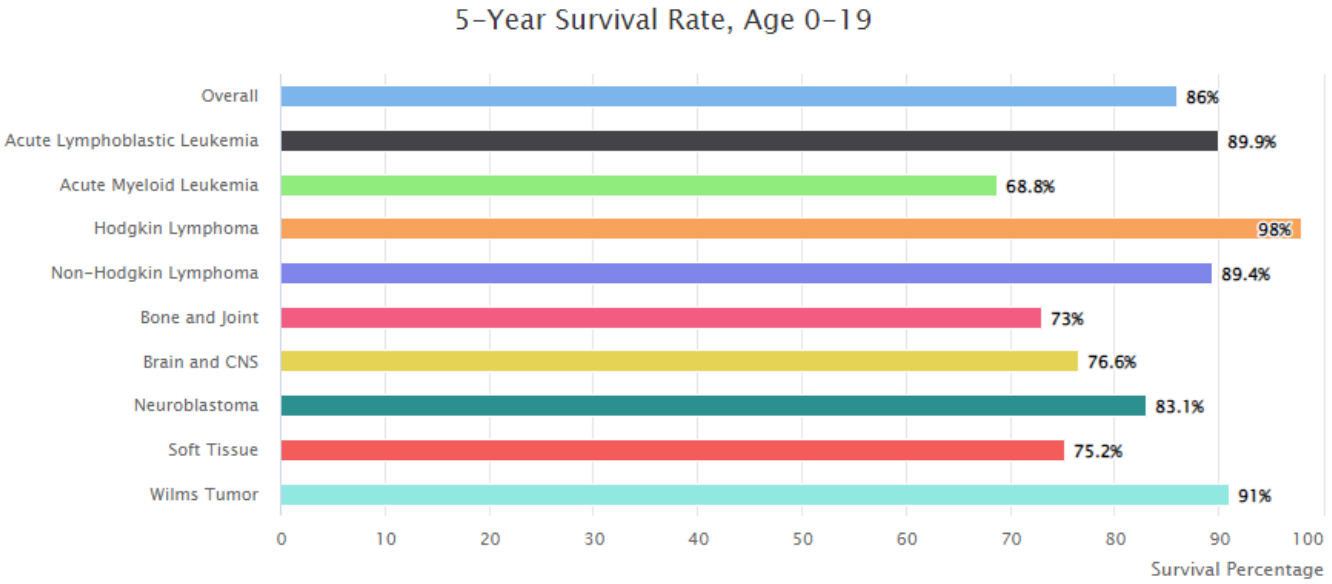
American Cancer Society, Surveillance Research, 2014

1) https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2014.html

Childhood Cancer

In the last 40 years, the overall survival rate for children's cancer has increased from 10% to nearly 85% today, but for many more rare childhood cancers, the survival rate is much less

- 12% of children who are diagnosed with cancer do not survive
- There are approximately 483,000 adult survivors of children's cancer in the United States



1) https://curesearch.org/5-year-survival-rateSource: NCCR*Explorer: An interactive website for NCCR cancer statistics [Internet]. National Cancer Institute. [Cited 2021 October 30]. Available from NCCRExplorer.ccdi.cancer.gov Years: 2011-2017

https://curesearch.org/

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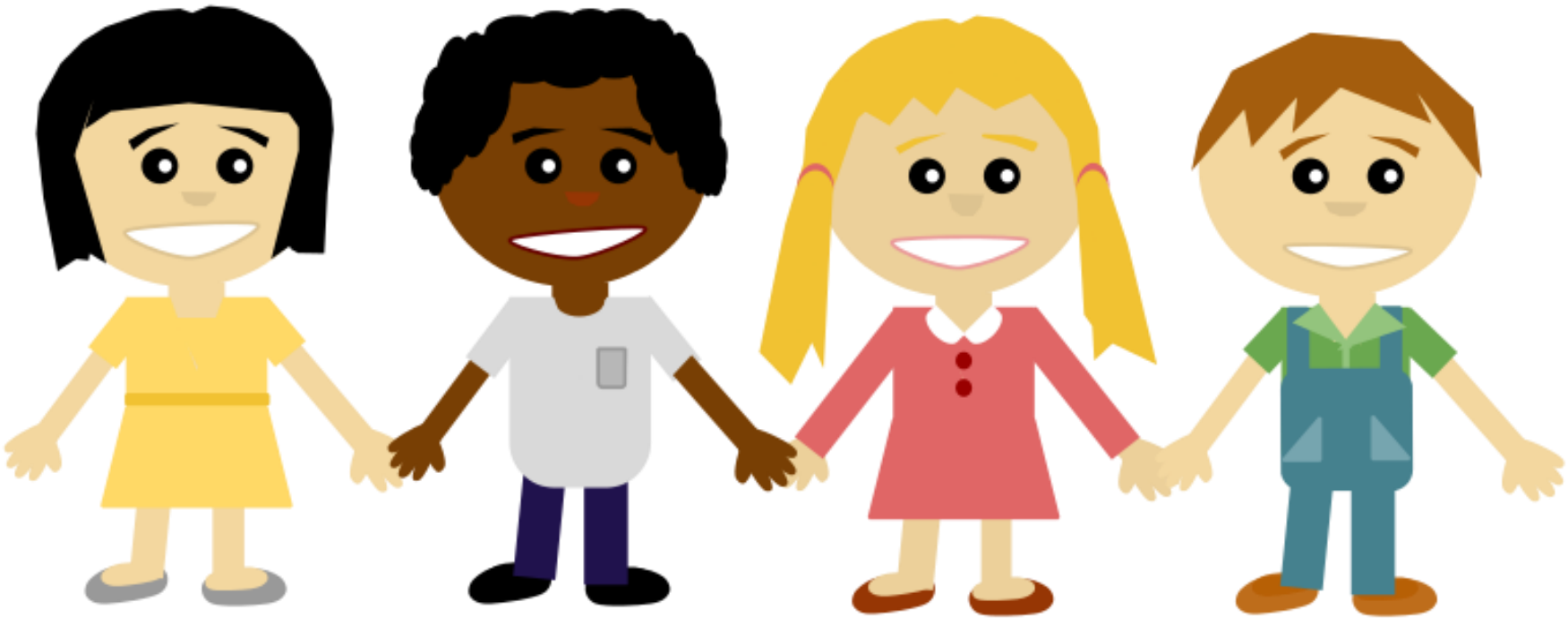
Childhood Cancer

Cancer in 0-14 yrs



Childhood Cancer: 0-14 yrs

Acute Lymphoblastic Leukemia

Most common childhood cancer (~30%). 5x's more common than AML

Most common presentation is between 2-5 yrs. Best prognosis is 1-9 years.

Pallor, fever, bleeding/bruising, hepatosplenomegaly, lymphadenopathy (~30%)

Treatment consists of: induction, consolidation, and maintenance. Includes therapy directed toward CNS.

Neurotoxicity is a risk. Attempts to lower radiation to the CNS and drugs to the CNS.

Relapse at <18 months from primary disease has ~21% 5 year survival. Monitor for relapse in bone marrow, CNS, and testicle.

Childhood Cancer: 0-14 yrs

Acute Lymphoblastic Leukemia

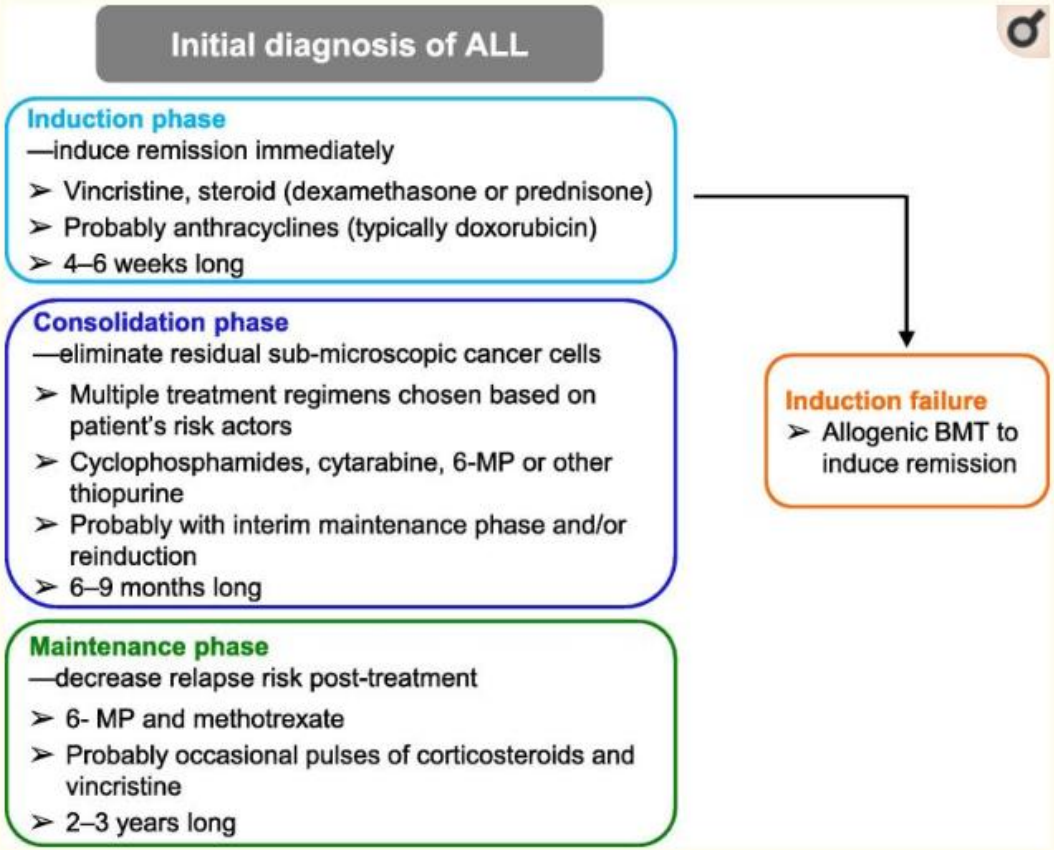


Figure 1

Diagram of the treatment phases of pediatric acute lymphocytic leukemia

Rudin, Shoshana, Marcus Marable, and R. Stephanie Huang. "The promise of pharmacogenomics in reducing toxicity during acute lymphoblastic leukemia maintenance treatment." *Genomics, proteomics & bioinformatics* 15.2 (2017): 82-93.

Childhood Cancer: 0-14 yrs

Acute Lymphoblastic Leukemia

Late effects include:

- Neurodevelopmental impairment
- Growth retardation
- Cardiotoxicity
- Risk for second malignancies (2-3%, 2nd leukemia, brain tumors)
- Endocrinopathies
- Infertility

Childhood Cancer: 0-14 yrs

Acute Lymphoblastic Leukemia

NIH NATIONAL CANCER INSTITUTE www.cancer.gov

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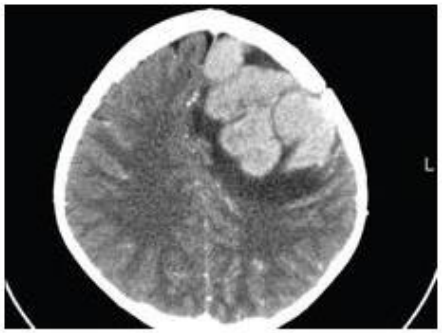
Children with Acute Lymphoblastic Leukemia Can Skip Radiation to the Brain

11/25/2019



Only 1.5% of children with acute lymphoblastic leukemia who skipped radiation had a recurrence in the central nervous system, according to a recent trial. The therapy, which is intended to prevent such a recurrence, can have devastating side effects.

AYA Cancer

Cancer in 15-39 yrs

AYA Cancer: 15-39 yrs

Hodgkin Lymphoma

Most common childhood cancer in the 15-19 age group. 5 year survival ~ 94%.

Incidence peaks in young adults and older adults.

Fatigue, anorexia, weight loss, fever, lymphadenopathy, mediastinal mass.

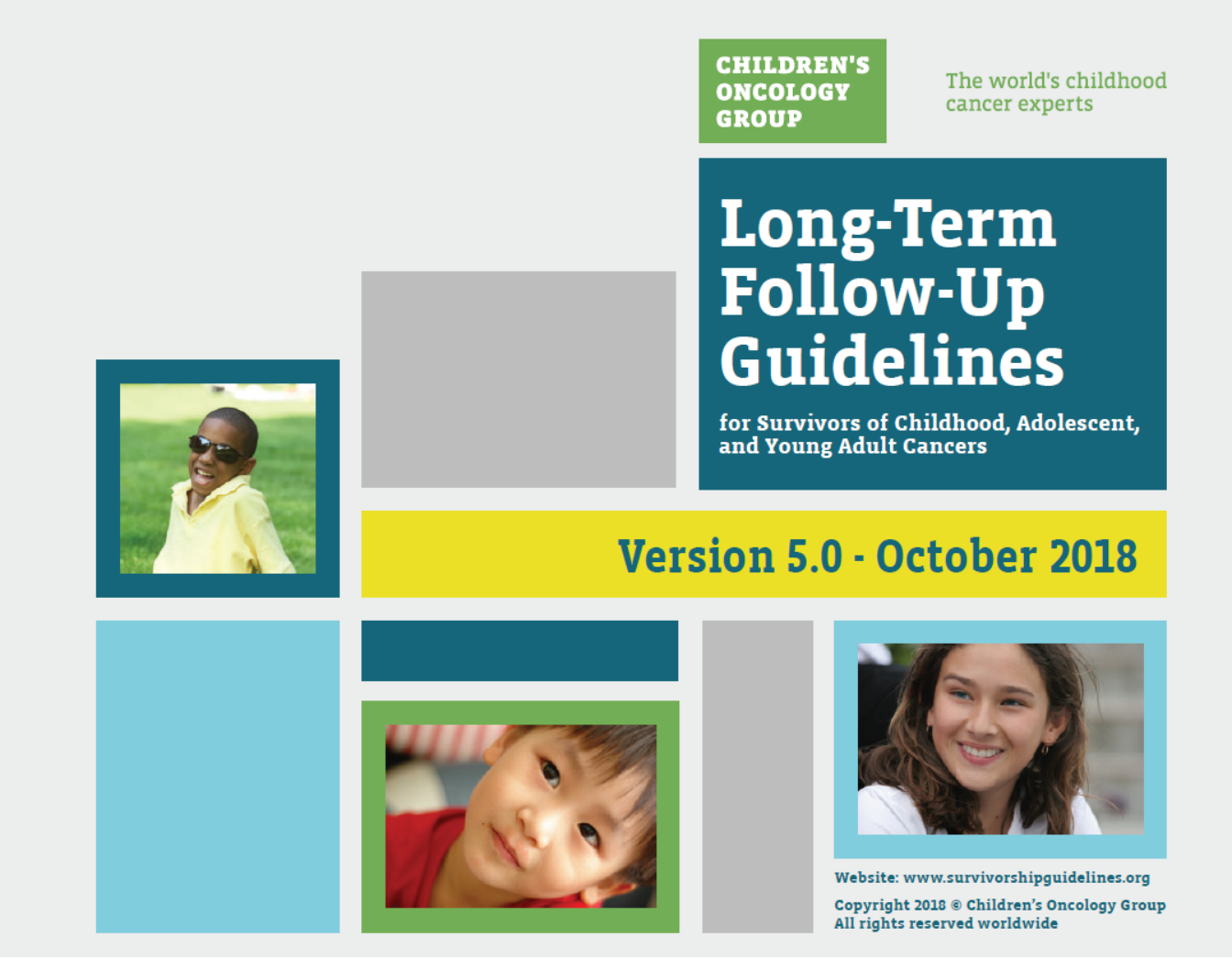
Risk stratification determines start treatment. Low-, intermediate-, and high-risk disease. Currently, treatment includes chemotherapy +/- radiation. Treatment is adjusted by response.

Acute toxicities include infection, neuro-, cardio-, and pulmonary-toxicity.

Long term mortality of 5-year survivors. 5.8% died within 15 years. (½ by disease progression, and ½ by long-term toxicities). Common problems include fertility issues, cardiac disease (chest radiation), and second malignancies.

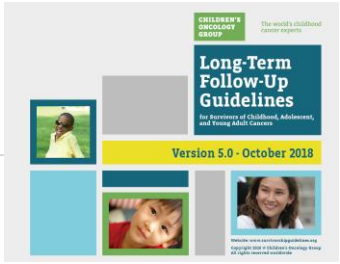
Childhood and AYA Cancer

Long-Term Follow-up



www.survivorshipguidelines.org

Childhood and AYA Cancer



Toxicities/Complications of chemotherapy

Any chemo
Dental abnormalities

Heavy metals
Ototoxicity, peripheral neuropathy, renal toxicity

Antimetabolites
Neurocognitive deficits, hepatic dysfunction, low bone mineral density

Alkylating agents
reproductive abnormalities Myelodysplasia, leukemia, pulmonary fibrosis, cataracts, urinary tract toxicity/malignancy

Anthracycline antibiotics
AML, cardiac toxicity

Antitumor antibiotics
Pulmonary toxicity

Steroids
Low bone mineral density, osteonecrosis, cataracts

Childhood and AYA Cancer

Toxicities/Complications of radiation

Dependent on the field

Brain/cranium
Neurocognitive deficits, CVAs, craniofacial abnormalities

Neuroendocrine axis
Obesity, growth hormone deficiency, precocious puberty, central endocrinopathies

All fields
Secondary benign or malignant neoplasm, dermatologic toxicity

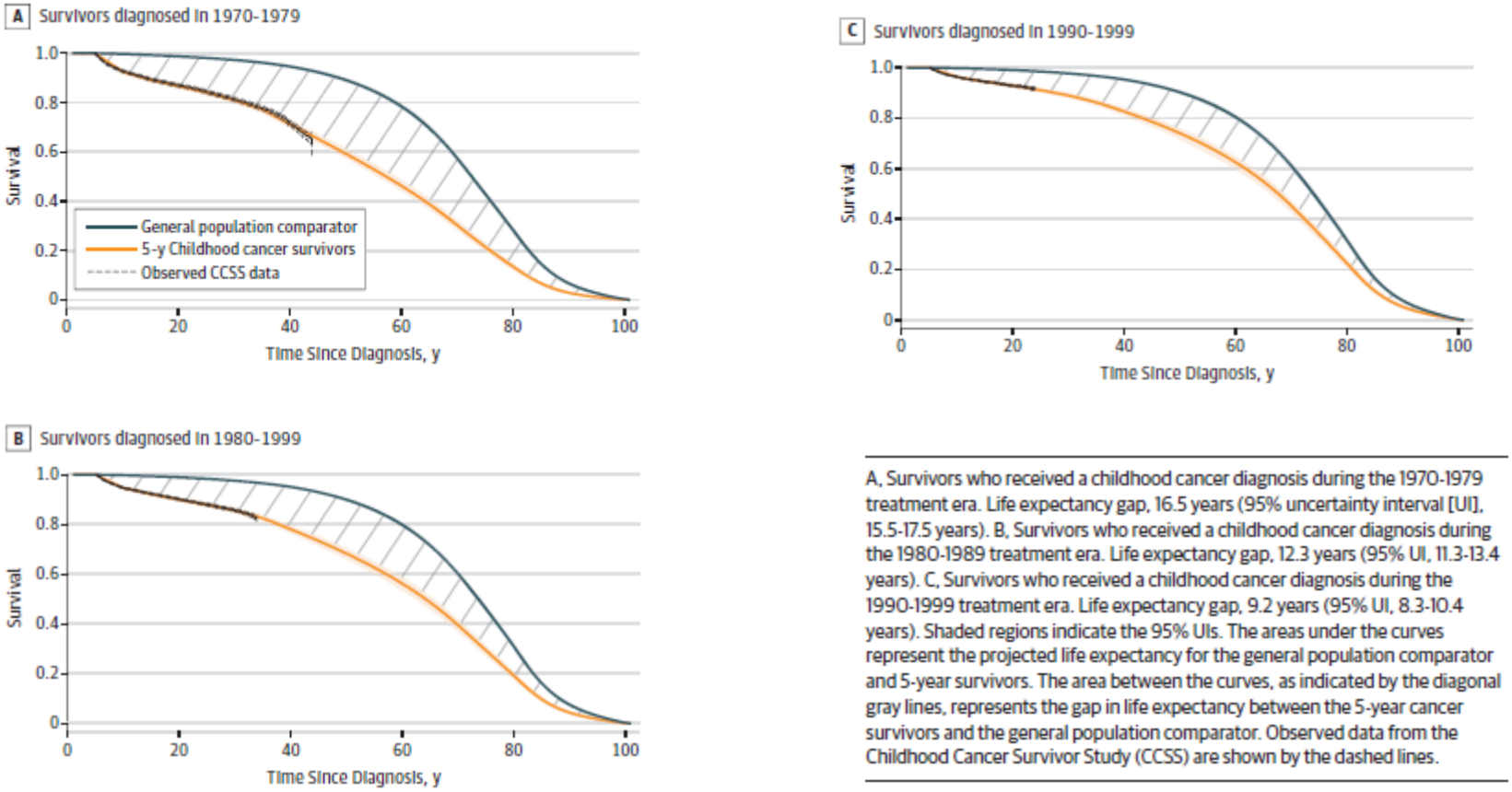
Torso
Breast, thyroid, pulmonary, cardiac toxicities

Abdomen/pelvis
Strictures, hepatic toxicity, bowel obstruction, fistulas, renal toxicity, reproduction abnormalities

Musculoskeletal system
Growth problems, scoliosis, radiation-induced fractures

Childhood Cancer

Figure 1. Projected Survival Curves for Childhood Cancer Survivors and General Population Comparators



A, Survivors who received a childhood cancer diagnosis during the 1970-1979 treatment era. Life expectancy gap, 16.5 years (95% uncertainty interval [UI], 15.5-17.5 years). B, Survivors who received a childhood cancer diagnosis during the 1980-1989 treatment era. Life expectancy gap, 12.3 years (95% UI, 11.3-13.4 years). C, Survivors who received a childhood cancer diagnosis during the 1990-1999 treatment era. Life expectancy gap, 9.2 years (95% UI, 8.3-10.4 years). Shaded regions indicate the 95% UIs. The areas under the curves represent the projected life expectancy for the general population comparator and 5-year survivors. The area between the curves, as indicated by the diagonal gray lines, represents the gap in life expectancy between the 5-year cancer survivors and the general population comparator. Observed data from the Childhood Cancer Survivor Study (CCSS) are shown by the dashed lines.

Yeh, Jennifer M., et al. "Life Expectancy of Adult Survivors of Childhood Cancer Over 3 Decades." *JAMA oncology* (2020).

Childhood Cancer and Cancer Survivorship

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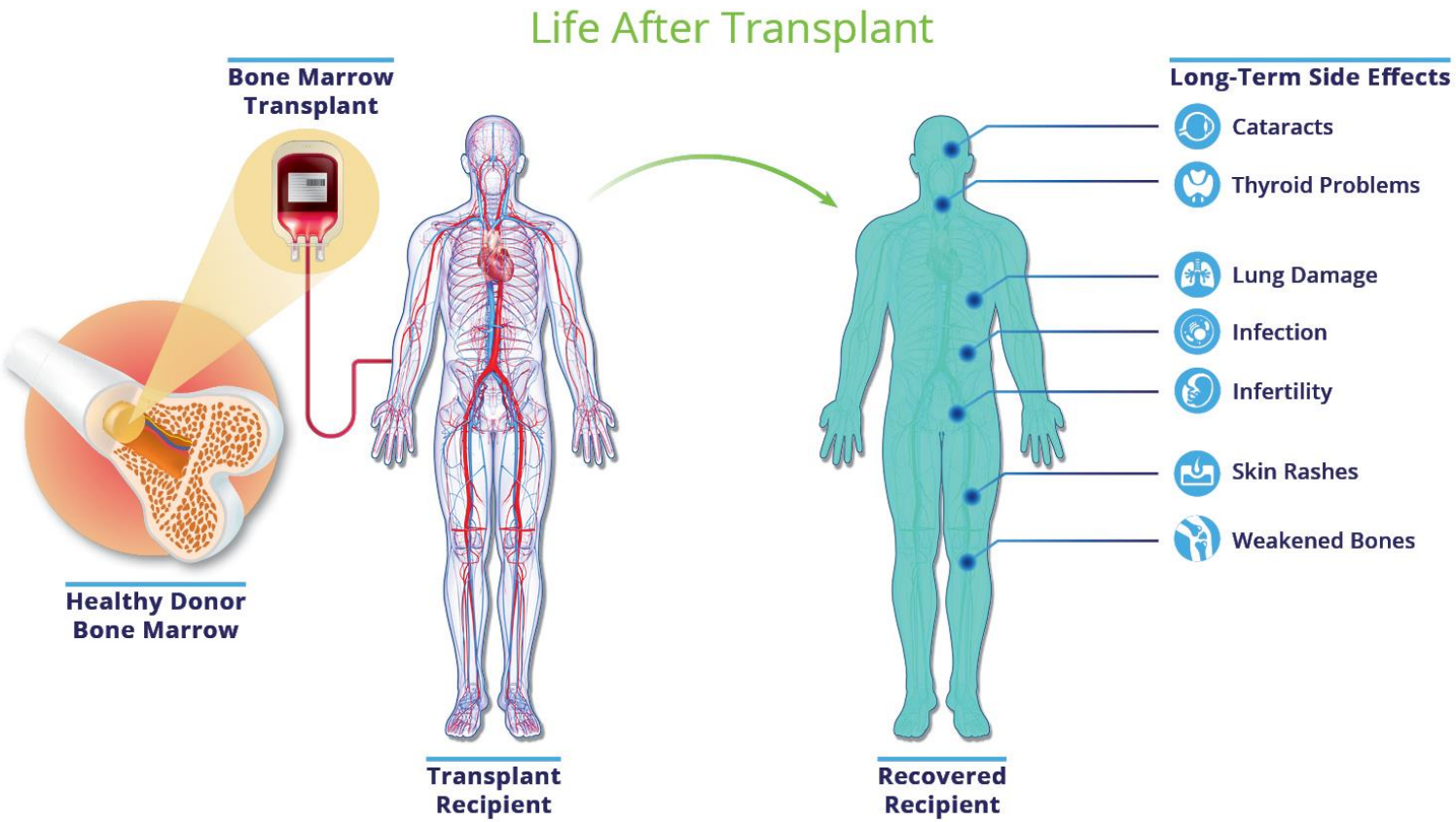
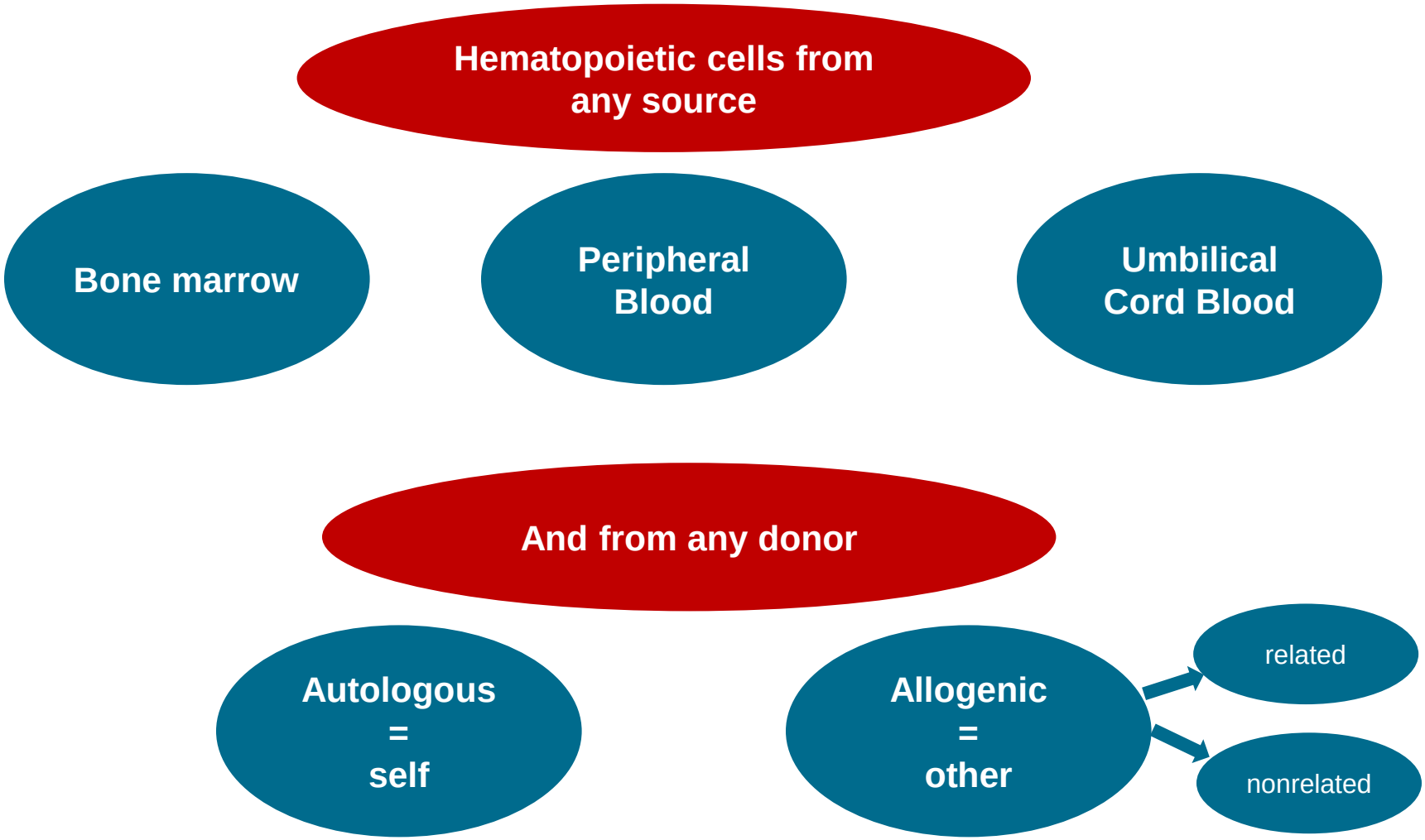
Hematopoietic Cell Transplantation (HCT)



1) https://www.pcori.org/research-results/pcori-stories/bone-marrow-transplants-more-just-survival

Hematopoietic Cell Transplantation (HCT)



1) https://curesearch.org/Childhood-Cancer-Statistics

When Is HCT used?

Stem cell transplants are used for …

- Leukemias
- Lymphomas
- Multiple myeloma
- Testicular cancer
- Neuroblastoma
- Myelodysplastic syndrome
- Aplastic anemia
- Sickle Cell disease
- Thalassemia

Being looked at …

- Systemic lupus erythematosus (SLE)
- Crohn's disease
- Multiple sclerosis (MS)

1) https://curesearch.org

HCT

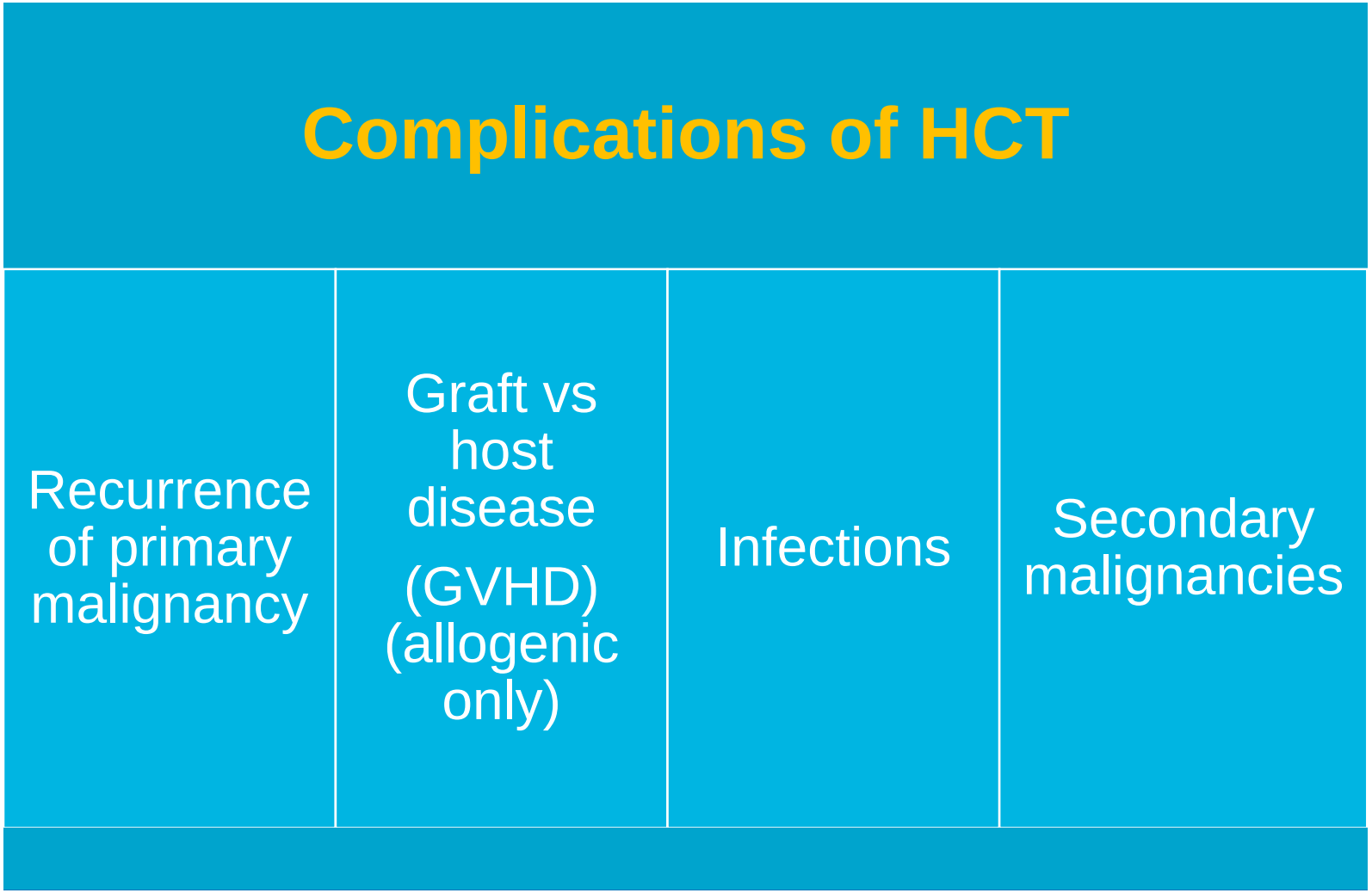
- The goal is to kill all cancer cells before transplant, using chemo and radiation.

- Autologous stem cell transplant
  - Get your own cells back, therefore no graft vs host disease.
  - Cannot get graft vs cancer effect (beneficial effect).
  - Cancer cells might be collected when collecting stem cells during harvest.
  - The immune system is the same as pre-transplant, it already let some cancer through.
  - Can still have graft failure.

- Allogenic stem cell transplant
  - Donor stem cells make their own immune cells ie. graft-versus-cancer effect.
  - Donor can donate more stem cells or WBCs if needed.
  - Graft might not take.
  - Risk of graft vs host disease (GVHD)
  - Infection

1) https://curesearch.org

Hematopoietic Cell Transplantation (HCT)

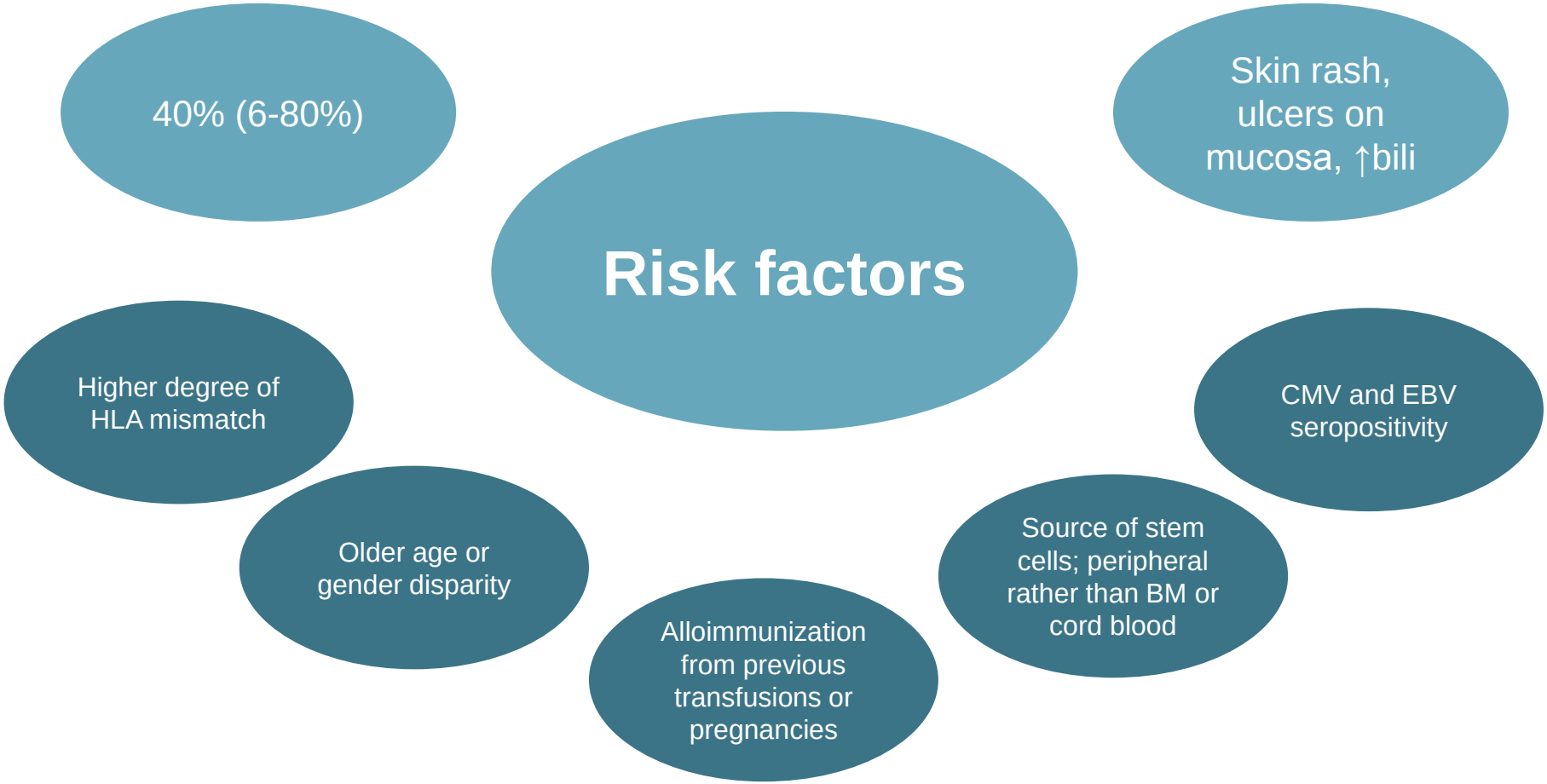


1) https://curesearch.org/

Hematopoietic Cell Transplantation (HCT)

Chronic graft vs host disease (GVHD)

allogenic only



Childhood Cancer and Cancer Survivorship

AGENDA

1. Epidemiology of Cancer Survivorship
2. Childhood Cancers
3. Hematopoietic Cell Transplant (HCT) Review
4. **Childhood HCT**
5. Adult HCT
6. Review
7. Questions

Hematopoietic Cell Transplantation (HCT)

TRANSPLANTATION

Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 report

Anna Sällfors Holmqvist,[1,2] Yanjun Chen,[3] Jessica Wu,[3] Kevin Battles,[3] Ravi Bhatia,[4] Liton Francisco,[3] Lindsey Hageman,[3] Michelle Kung,[3] Emily Ness,[3] Mariel Parman,[3] Donna Salzman,[4] Jeanette Falck Winther,[5,6] Joseph Rosenthal,[7] Stephen J. Forman,[7] Daniel J. Weisdorf,[8] Mukta Arora,[8] Saro H. Armenian,[7] and Smita Bhatia[3]

Autologous HCT performed in one of the two participating US centers on patients <22 years old, who had survived for 2 years

Overall survival calculated using Kaplan-Meier techniques

345 2-year survivors, 103 deaths observed

1) Holmqvist, Anna Sällfors, et al. "Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 report." *Blood* 131.24 (2018): 2720-2729.

Hematopoietic Cell Transplantation (HCT)

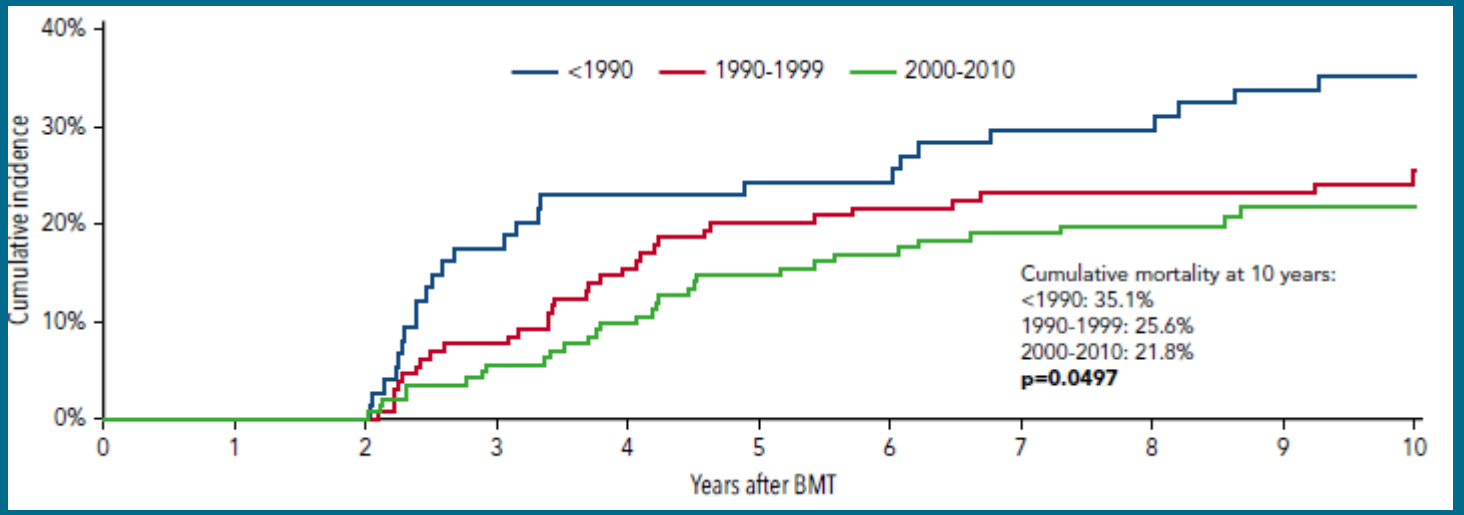
Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 Report

Variables	Entire cohort		Primary diagnosis											
			ALL		AML		HL		NHL		Neuroblastoma		Other malignant disease*	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	345	100.0	43	12.5	45	13.0	90	26.1	31	9.0	79	22.9	57	16.5
Sex														
Male	212	61.4	34	79.1	24	53.3	52	57.8	22	71.0	49	62.0	31	54.4
Female	133	38.6	9	20.9	21	46.7	38	42.2	9	29.0	30	38.0	26	45.6
Race/ethnicity														
Non-Hispanic white	264	76.5	36	83.7	35	77.8	59	65.6	25	80.6	64	81.0	45	78.9
Hispanic	44	12.8	3	7.0	5	11.1	18	20.0	1	3.2	9	11.4	8	14.0
Non-Hispanic black	20	5.8	3	7.0	4	8.9	7	7.8	3	9.7	2	2.5	1	1.8
Other	10	2.9	1	2.3	1	2.2	4	4.4	1	3.2	2	2.5	1	1.8
Unknown	7	2.0	0	0.0	0	0.0	2	2.2	1	3.2	2	2.5	2	3.5
Age at BMT, y														
0-4	97	28.1	13	30.2	11	24.4	0	0.0	1	3.2	59	74.7	13	22.8
5-9	57	16.5	15	34.9	6	13.3	3	3.3	6	19.4	14	17.7	13	22.8
10-14	55	15.9	6	14.0	10	22.2	15	16.7	4	12.9	3	3.8	17	29.8
15-21	136	39.4	9	20.9	18	40.0	72	80.0	20	64.5	3	3.8	14	24.6
Year of BMT														
<1990	74	21.4	34	79.1	12	26.7	11	12.2	9	29.0	7	8.9	1	1.8
1990-1999	129	37.4	9	20.9	25	55.6	32	35.6	11	35.5	31	39.2	21	36.8
2000-2010	142	41.2	0	0.0	8	17.8	47	52.2	11	35.5	41	51.9	35	61.4
Source of stem cells														
Bone marrow	163	47.2	41	95.3	32	71.1	30	33.3	15	48.4	32	40.5	13	22.8
PBSCs	181	52.5	2	4.7	13	28.9	60	66.7	16	51.6	47	59.5	43	75.4
Cord blood	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.8

1) Holmqvist, Anna Sällfors, et al. "Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 report." *Blood* 131.24 (2018): 2720-2729.

Hematopoietic Cell Transplantation (HCT)

Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 Report



- Conditional on surviving the first 2 years….
- Median follow up 14.2 years (2.0-35.3 years)
- Median age at death 19.9 years (4.1-36.7 years)
- Overall survival at 5, 10, and 15 years after transplantation 81.2%, 73.8%, and 70.3%

1) Holmqvist, Anna Sällfors, et al. "Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 report." *Blood* 131.24 (2018): 2720-2729.

Hematopoietic Cell Transplantation (HCT)

Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 Report

Overall survival at each additional 5 y after BMT, y	Entire cohort		Primary diagnosis					
	N	%	ALL %	AML %	HL %	NHL %	Neuroblastoma %	Other malignant disease* %
2+	280	81.2	67.4	95.6	86.7	90.3	78.5	71.9
5+	207	90.9	89.7	95.4	88.7	96.3	89.4	88.4
10+	162	95.3	96.2	97.5	95.3	82.0	97.6	100.0
15+	196	99.3	100.0	100.0	96.6	100.0	100.0	100.0

*Includes 25 Ewing sarcomas, 11 Wilms tumor, 9 CNS tumors, 4 desmoplastic small round cell tumors, 6 soft tissue sarcoma, 1 ovarian tumor, 1 hepatoblastoma, and 1 multiple myeloma.

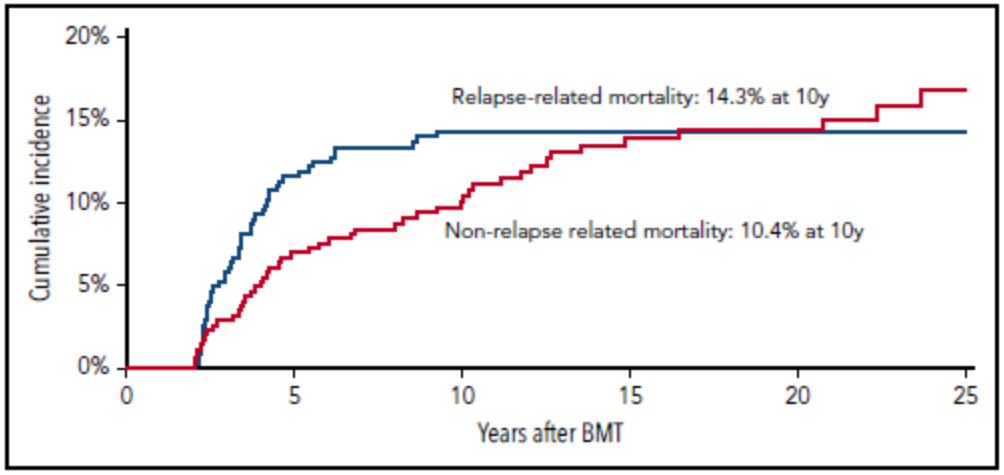
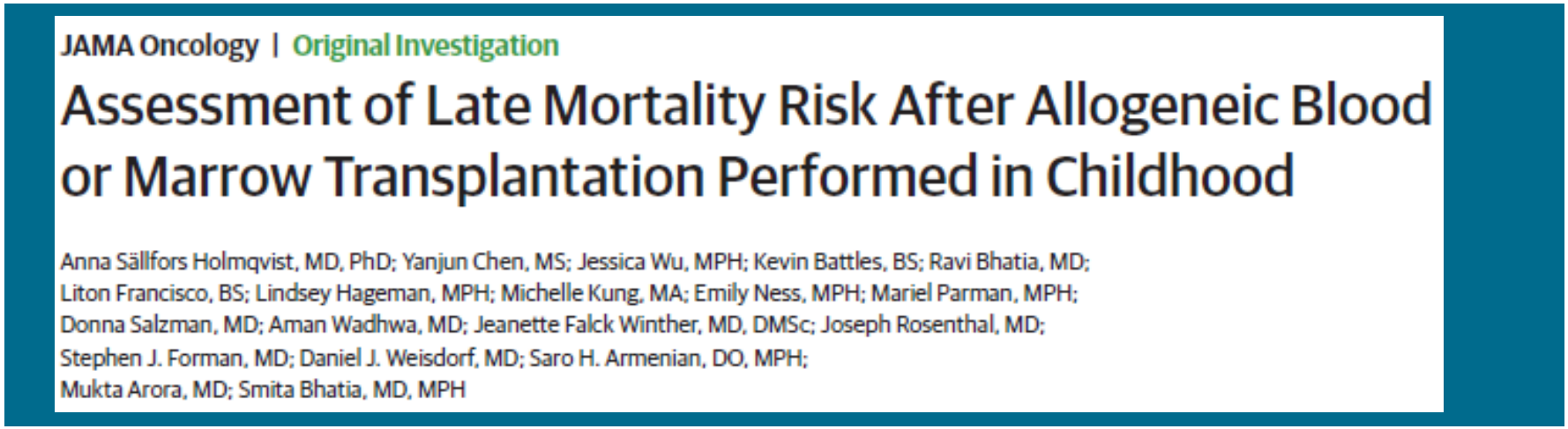


Figure 2. Cumulative RRM and NRM in 345 patients undergoing autologous BMT in childhood and surviving $\geq$2 years

1) Holmqvist, Anna Sällfors, et al. "Late mortality after autologous blood or marrow transplantation in childhood: a Blood or Marrow Transplant Survivor Study-2 report." *Blood* 131.24 (2018): 2720-2729.

Hematopoietic Cell Transplantation (HCT)

Assessment of Late Mortality Risk after Allogeneic Blood or Marrow Transplantation Performed in Childhood



- **Allogenic HCT performed in one of the two participating US centers on patients <22 years old, who had survived for 2 years between 1974-2010**
- **Overall survival calculated using Kaplan-Meier techniques**
- **1388 2-year survivors, 295 deaths observed**

1) Holmqvist, Anna Sällfors, et al. "Assessment of Late Mortality Risk After Allogeneic Blood or Marrow Transplantation Performed in Childhood." *JAMA oncology* 4.12 (2018): e182453-e182453.

Hematopoietic Cell Transplantation (HCT)

Assessment of Late Mortality Risk after Allogeneic Blood or Marrow Transplantation Performed in Childhood

Table 1. Demographic and Clinical Characteristics of Individuals Who Lived 2 Years or More After Allogeneic BMT Performed in Childhood

Variable	Patients, No. (%) (N = 1388)
Treating institution	
University of Minnesota	950 (68.4)
City of Hope	438 (31.6)
Sex	
Male	829 (59.7)
Female	559 (40.3)
Race/ethnicity	
Non-Hispanic white	982 (70.7)
Hispanic	213 (15.3)
Non-Hispanic black	71 (5.1)
Other	96 (6.9)
Unknown	26 (1.9)
Age at BMT, y	
≥4	379 (27.3)
5-9	362 (26.1)
10-14	266 (19.2)
15-21	381 (27.4)
Time period of BMT	
<1990	323 (23.3)
1990-1999	407 (29.3)
2000-2010	658 (47.4)
Type of donor	
Related	803 (57.9)
Unrelated	585 (42.1)
Source of stem cells	
Bone marrow	1019 (73.4)
Cord blood	253 (18.2)
PBSCs	116 (8.4)
Primary disease	
ALL	348 (25.1)
AML or MDS	326 (23.5)
Inborn errors of metabolism	192 (13.8)
Severe aplastic anemia	147 (10.6)
Fanconi anemia[a]	115 (8.3)
Chronic myelogenous leukemia	90 (6.5)
Immune disorders	55 (4.0)
Sickle cell disease or thalassemia	26 (1.9)
Other malignant disease[b]	64 (4.6)
Other nonmalignant disease[c]	25 (1.8)
Conditioning regimen	
Cyclophosphamide	1118 (80.5)
Total body irradiation	892 (64.3)
Antithymocyte globulin	563 (40.6)
Busulfan	355 (25.6)
Fludarabine	251 (18.1)
Etoposide	216 (15.6)
Melphalan	68 (4.9)
Cytarabine	58 (4.2)
Other chemotherapy	126 (9.1)
Other radiotherapy	84 (6.1)
Total body irradiation plus cyclophosphamide	691 (49.8)
Busulfan plus cyclophosphamide	326 (23.5)
Disease status at BMT	
Standard risk of relapse[d]	742 (53.5)
High risk of relapse	642 (46.3)
Chronic GvHD prophylaxis	
Yes	1361 (98.1)
Cyclosporine	953 (68.7)
Methotrexate	777 (56.0)
Systemic corticosteroids	582 (41.9)
Mycophenolic acid	206 (14.8)
T-cell depletion	190 (13.7)
Tacrolimus or sirolimus	99 (7.1)
No. of deaths	295 (21.3)

1) Holmqvist, Anna Sällfors, et al. "Assessment of Late Mortality Risk After Allogeneic Blood or Marrow Transplantation Performed in Childhood." *JAMA oncology* 4.12 (2018): e182453-e182453.

Hematopoietic Cell Transplantation (HCT)

Assessment of Late Mortality Risk after Allogeneic Blood or Marrow Transplantation Performed in Childhood

Table 2. SMR and AER Among 1388 Individuals Who Lived 2 Years or More After Allogeneic BMT in Childhood

Variable	Entire Cohort, No. of Patients	All-Cause Mortality (95% CI)	
		SMR	AER
All patients	1388	14.4 (12.8 to 16.1)	12.0 (10.5 to 13.5)
Sex			
Male	829	11.2 (9.6 to 13.0)	11.5 (9.6 to 13.4)
Female	559	23.6 (19.6 to 28.0)	12.7 (10.4 to 15.1)
Age at BMT, y			
≤4	379	20.3 (15.8 to 25.7)	9.6 (7.1 to 12.0)
5-9	362	22.8 (17.9 to 28.4)	12.9 (9.8 to 16.0)
10-14	266	12.8 (9.8 to 16.3)	11.9 (8.6 to 15.2)
15-21	381	10.3 (8.4 to 12.5)	13.8 (10.8 to 16.9)
Time period of BMT			
<1990	323	12.6 (10.6 to 14.9)	15.0 (12.3 to 17.8)
1990-1999	407	13.6 (10.9 to 16.6)	10.3 (7.9 to 12.6)
2000-2010	658	20.8 (16.4 to 25.9)	10.4 (7.9 to 12.9)
Type of donor			
Related	803	12.8 (11.1 to 14.7)	12.6 (10.7 to 14.4)
Unrelated	585	19.9 (16.0 to 24.3)	11.0 (8.6 to 13.3)
Source of stem cells			
Bone marrow	1019	13.4 (11.8 to 15.2)	12.1 (10.4 to 13.7)
Cord blood	253	21.2 (14.3 to 30.0)	9.3 (5.7 to 12.8)
PBSC	116	22.5 (14.5 to 32.9)	17.8 (10.2 to 25.4)

Table 2. SMR and AER Among 1388 Individuals Who Lived 2 Years or More After Allogeneic BMT in Childhood

Variable	Entire Cohort, No. of Patients	All-Cause Mortality (95% CI)	
		SMR	AER
Primary diagnosis			
ALL	348	18.5 (15.1 to 22.4)	17.3 (13.7 to 20.9)
AML or MDS	326	13.3 (10.5 to 16.7)	11.6 (8.6 to 14.5)
Inborn errors of metabolism	192	28.2 (20.6 to 37.5)	14.6 (10.1 to 19.2)
Severe aplastic anemia	147	4.6 (2.8 to 7.0)	4.3 (1.8 to 6.9)
Fanconi anemia[a]	115	21.0 (11.6 to 34.6)	9.3 (4.0 to 14.6)
Chronic myelogenous leukemia	90	11.8 (7.3 to 17.9)	11.5 (5.8 to 17.1)
Other malignant disease[b]	64	14.0 (7.9 to 22.7)	13.8 (6.0 to 21.6)
Immune disorders	55	9.3 (4.0 to 18.0)	5.6 (1.0 to 10.2)
Sickle cell disease or thalassemia	26	24.1 (6.0 to 62.5)	9.1 (-1.6 to 19.7)
Other nonmalignant disease[c]	25	37.9 (15.1 to 76.8)	19.9 (3.6 to 36.3)
Disease status at BMT			
Standard risk of relapse[d]	742	10.3 (9.4 to 11.3)	9.9 (8.1 to 11.7)
High risk of relapse	642	23.3 (21.2 to 25.6)	15.1 (12.6 to 17.6)
Overall survival after BMT, y			
2-5	142	522.0 (439.9 to 613.6)	310.8 (259.0 to 362.6)
6-9	337	35.9 (26.3 to 47.6)	15.0 (10.5 to 19.6)
10-14	281	14.5 (10.0 to 20.0)	7.9 (5.0 to 10.9)
15-19	218	9.1 (6.1 to 13.0)	6.0 (3.5 to 8.5)
20-24	164	5.8 (3.6 to 8.8)	4.3 (2.0 to 6.6)
≥25	246	2.9 (2.0 to 4.1)	2.6 (1.2 to 3.9)

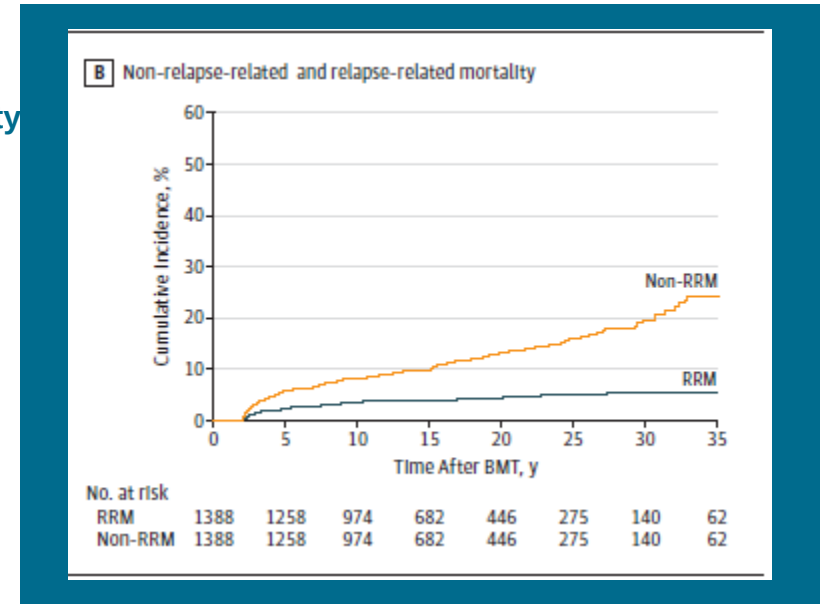
1) Holmqvist, Anna Sällfors, et al. "Assessment of Late Mortality Risk After Allogeneic Blood or Marrow Transplantation Performed in Childhood." *JAMA oncology* 4.12 (2018): e182453-e182453.

Hematopoietic Cell Transplantation (HCT)

Assessment of Late Mortality Risk after Allogeneic Blood or Marrow Transplantation Performed in Childhood

- Median age at transplantation 14.6 years (0-21)
- Overall survival rate at 20 years was 79.3%
- Overall 14.4-fold increased risk for death (95% 12.8-16.2)
- Leading causes of death
  - Infection and/or chronic graft-vs-host disease (GVH) 49.6%
  - Primary disease 24.6%
  - Subsequent malignant neoplasm 18.4%

- **RRM = relapse related mortality**

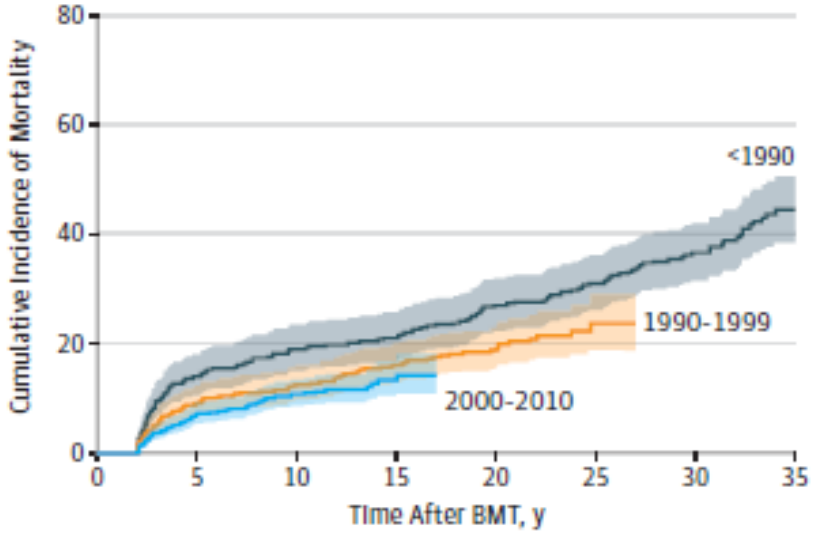


1) Holmqvist, Anna Sällfors, et al. "Assessment of Late Mortality Risk After Allogeneic Blood or Marrow Transplantation Performed in Childhood." *JAMA oncology* 4.12 (2018): e182453-e182453.

Hematopoietic Cell Transplantation (HCT)

Assessment of Late Mortality Risk after Allogeneic Blood or Marrow Transplantation Performed in Childhood

Figure 2. Cumulative All-Cause Mortality of 1388 Individuals Who Lived 2 Years or More After Allogeneic Blood or Marrow Transplantation (BMT) Performed in Childhood, by Treatment Time Period



No. at risk								
<1990	323	278	262	255	236	223	140	62
1990-1999	407	369	355	340	210	52	0	0
2000-2010	658	611	357	87	0	0	0	0

Cumulative incidence of mortality at 10 years (18.9% prior to 1990, 12.9% in 1990-1999, and 11.0% in 2000-2010; $P = .002$). The shaded areas indicate 95% CIs.

1) Holmqvist, Anna Sällfors, et al. "Assessment of Late Mortality Risk After Allogeneic Blood or Marrow Transplantation Performed in Childhood." *JAMA oncology* 4.12 (2018): e182453-e182453.

Hematopoietic Cell Transplantation (HCT)

Original Article*

Late mortality after hematopoietic SCT for a childhood malignancy

- **Patients aged 0-19.9 years who received HCT at Hospital for Sick Children in Ontario and survived 2 years 1985-2008**
- **Included only those with cancer**
- **Overall survival calculated using Kaplan-Meier techniques**
- **479 2 yr survivors, 98 deaths observed**

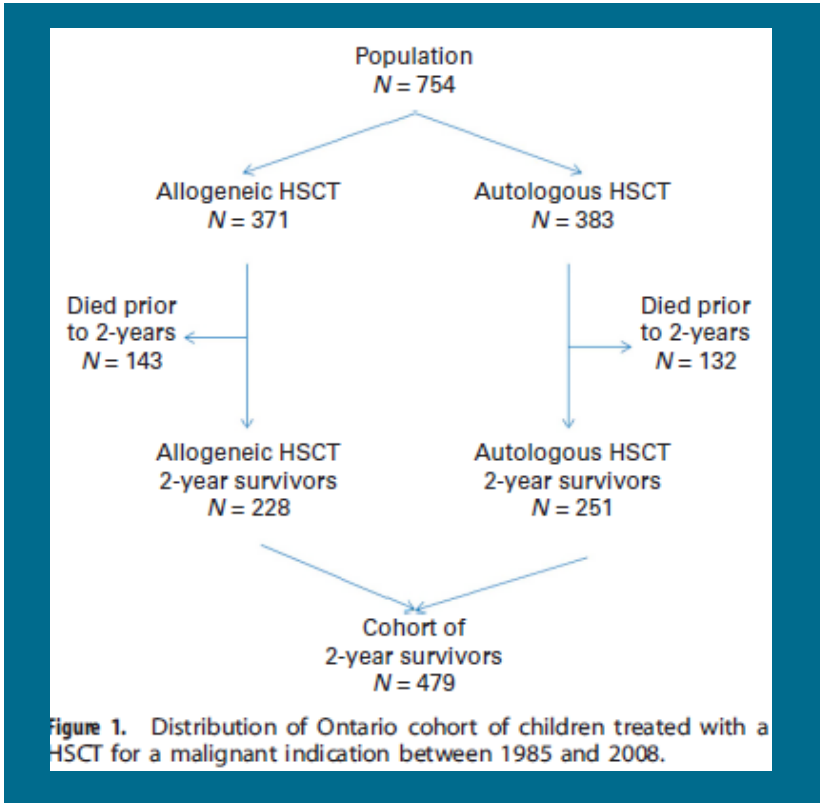


Figure 1. Distribution of Ontario cohort of children treated with a HSCT for a malignant indication between 1985 and 2008.

* Schechter, T., et al. "Late mortality after hematopoietic SCT for a childhood malignancy." *Bone marrow transplantation* 48.10 (2013): 1291.

Hematopoietic Cell Transplantation (HCT)

Late mortality after hematopoietic SCT for a childhood malignancy

Allogenic HCT

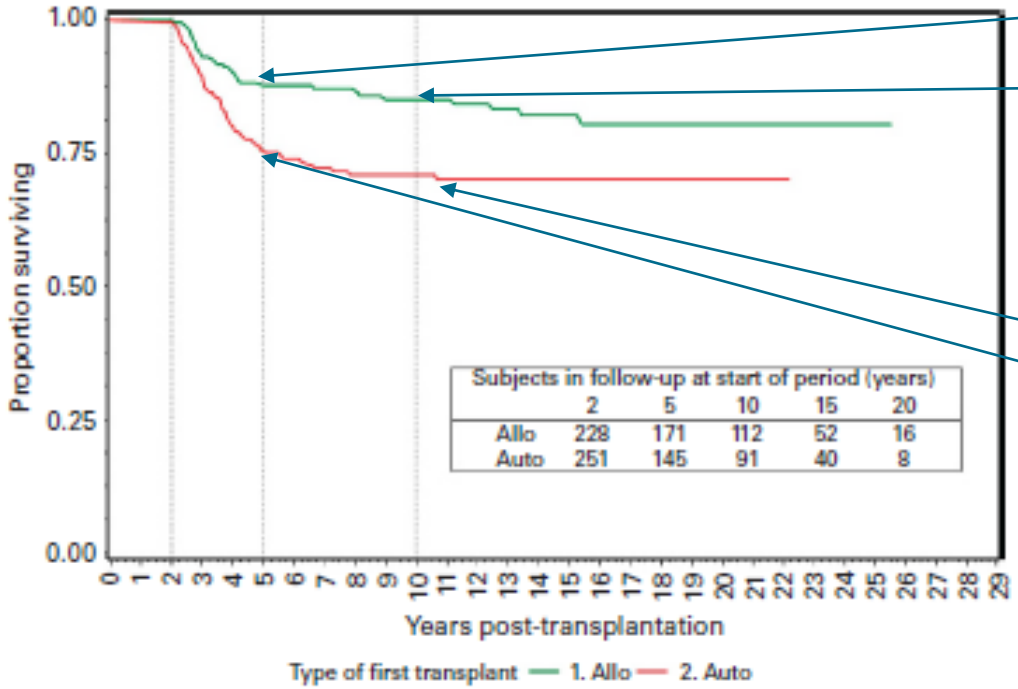
- 371 had HCT→ 228 (61.5%) were 2 year survivors
- Median follow up 10 yrs (2.0-25.6)
- Median age of survivors 8.0 yrs (0.3-19.0)
- Related-donor HCT 147 vs nonrelated donor 81
- 34/228 (14.9%) experienced a late death
- 64.7% of deaths were due to relapse of primary malignancy
- SMR of the 2 yr survivors → 370 (95% CI: 256-517)

Autologous HCT

- 383 had HCT → 251 (65.5%) were 2 year survivors
- Median follow up 6.7 yrs (2.0-22.2)
- 64/251 (25.5%) experienced a late death
- 89% of deaths were due to recurrence of primary malignancy
- Median time of late death 6.7 years after HCT (range 2.0-22.2 years)
- Patients with neuroblastoma comprised majority of cohort 98/251 (39%)
- SMR of the 2 yr survivors → 733 (95% CI: 565-937)

Hematopoietic Cell Transplantation (HCT)

Late mortality after hematopoietic SCT for a childhood malignancy



5 yr OS 88.2%

10 yr OS 85.1%

10 yr OS 71.0%

5 yr OS 75.6%

Figure 2. Kaplan–Meier survival curve for patients who underwent hematopoietic SCT in Ontario between 1985 and 2008, aged 0–19 years at the time of transplant, who survived at least 2 years from transplant by transplant type. Note: As zero years is considered the date of hematopoietic SCT and only 2-year survivors are included in this analysis, there are no deaths in the first 2 years of observation.

1) Schechter, T., et al. "Late mortality after hematopoietic SCT for a childhood malignancy." *Bone marrow transplantation* 48.10 (2013): 1291.

Hematopoietic Cell Transplantation (HCT)

Late mortality after hematopoietic SCT for a childhood malignancy

Table 2. Association between patient and transplant characteristics and late death among patients who underwent hematopoietic SCT in Ontario between 1985 and 2008, aged 0–19 years at the time of transplant and survived at least 2 years from transplant

Variables	*Autologous transplant (N = 251)*		*Allogeneic transplant (N = 228)*	
	Hazard ratio	*95% CI*	*Hazard ratio*	*95% CI*
Age groups				
0–3 years	1.00		1.00	
4–9 years	1.82	0.99–3.35	1.42	0.39–5.20
10 + years	1.74	0.72–4.18	2.02	0.58–7.01
Sex				
Female	1.00		1.00	
Male	1.84*	1.03–3.28	0.77	0.38–1.53
Year of transplantation				
Pre-1995	1.00		1.00	
1995–1999	0.86	0.32–2.31	1.22	0.44–3.38
2000–2004	1.06	0.39–2.84	2.09	0.67–6.48
2005–2008	0.69	0.21–2.27	1.44	0.38–5.41
Transplant type				
Related	—		1.00	
Unrelated	—		1.28	0.60–2.70
Primary diagnosis				
1. Leukemia	1.00		—	
ALL	—		1.00	
AML	—		0.59	0.22–1.56
Other leukemia	—		—	
2. Lymphoma	2.83	0.70–11.44	—	
3. CNS	2.49	0.46–13.53	—	
4. Neuroblastoma	9.03*	2.55–32.03	—	
5. Other	6.01*	1.53–23.62	0.48	0.14–1.59
Relapse pre-BMT	0.81	0.36–1.83	0.81	0.33–2.02
Conditioning				
Chemotherapy only	1.00		1.00	
Chemotherapy and TBI	2.33	0.88–6.22	1.13	0.41–3.10

Abbreviation: CI = confidence interval. Note: *P-value <0.05.

1) Schechter, T., et al. "Late mortality after hematopoietic SCT for a childhood malignancy." *Bone marrow transplantation* 48.10 (2013): 1291.

Childhood Cancer and Cancer Survivorship

AGENDA

1. Epidemiology of Cancer Survivorship
2. Childhood Cancers
3. Hematopoietic Cell Transplant (HCT) Review
4. Childhood HCT
5. **Adult HCT**
6. Review
7. Questions

Adult HCT

Reference	Data source and patients	Overall survival from HCT	Important risk factors for late mortality	Life expectancy
Autologous HCT				
Bhatia et al (2005)[7]	BMT SS, N=854 (≥ 2-yr survivors); auto HCT for ALL, AML, lymphoma	69% @ 10 yrs	Older age at HCT, disease with high relapse risk, diagnosis of ALL or lymphoma	Mortality rates approached that of general population by >10 yrs after HCT for patients with AML and standard risk disease
Majhail et al (2009)[9]	CIBMTR, N=1,367 (≥ 2-yr survivors); auto HCT for lymphoma	52-85% @ 10 yrs (varied by lymphoma type)	Older age at HCT	Mortality rates approached that of general population by 4 yrs after HCT
Majhail et al (2011)[14]	CIBMTR, N=315 (≥ 2-yr survivors); auto HCT for AML	94% @ 10 yrs	Older age at HCT, poor cytogenetic risk disease	Mortality rates higher than general population through 10 yrs after HCT
Vanderwalde et al (2013)[13]	Single center, N=2,388 (1,577 ≥2 yr survivors); auto HCT for lymphoma, myeloma, AML	5-year survival 75% for 2-yr survivors, 81% for 5-yr survivors, 88% for 10-yr survivors	Older age at HCT, disease at high risk for relapse	Mortality rates approached general population for 10-yr survivors, with exception of female Hodgkin lymphoma patients transplanted before 1995 at age ≤ 40 yrs

1) Majhail, Navneet S. "Long-term complications after hematopoietic cell transplantation." *Hematology/oncology and stem cell therapy* 10.4 (2017): 220-227.

Adult HCT

Reference	Data source and patients	Overall survival from HCT	Important risk factors for late mortality	Life expectancy
Allogeneic HCT				
Bhatia et al (2007)[6]	BMT SS, N=1,479, (≥ 2-yr survivors); MAC allo HCT for ALL, AML, CML, lymphoma, metabolic disorders, SAA	80% @15 yrs	Chronic GVHD, older age at HCT, disease with high relapse risk	Mortality rates higher than general population through 15 yrs after HCT
Goldman et al (2010)[8]	CIBMTR; N=2,444 (≥ 5-yr survivors); MAC allo HCT for CML	87-88% @ 15 yrs (varied by donor type)	Chronic GVHD	Mortality rates approached that of general population by 14 yrs after HCT
Wingard et al (2011)[11]	CIBMTR; N=10,632 (≥ 2-yr survivors); MAC allo HCT for ALL, AML, lymphoma, MDS, SAA	80-92% @ 10 yrs (varied by disease)	Chronic GVHD, older age at HCT, disease	Mortality rates higher than general population for most diseases through 15 yrs after HCT
Atsuta et al (2016)[15]	Japan Society for HCT, N=11,047 (≥ 2-yr survivors); MAC/RIC allo HCT for any diagnosis	83% @ 15 yrs	Chronic GVHD, older age at HCT, disease risk	Mortality rates higher than general population at 20 yrs after HCT

1) Majhail, Navneet S. "Long-term complications after hematopoietic cell transplantation." *Hematology/oncology and stem cell therapy* 10.4 (2017): 220-227.

Childhood Cancer and Cancer Survivorship

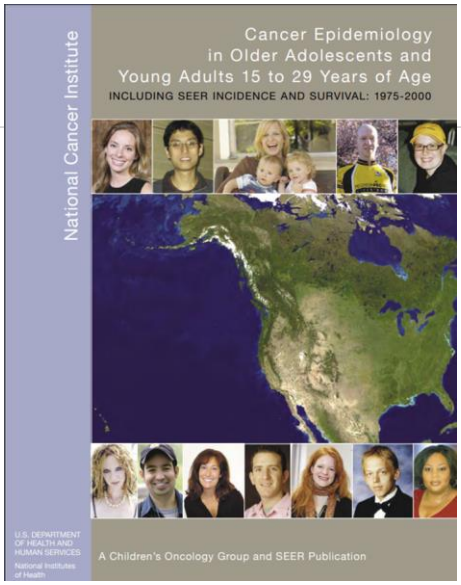
AGENDA

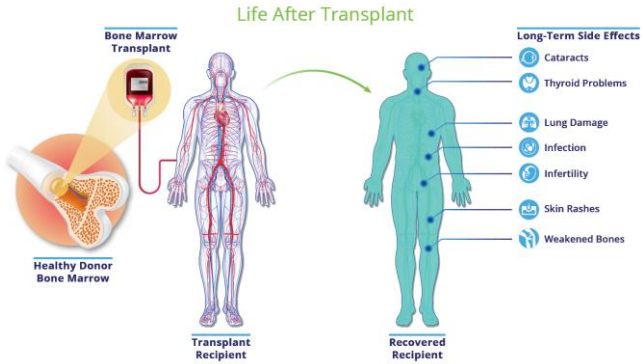
1. Epidemiology of Cancer Survivorship
2. Childhood Cancers
3. Stem Cell Transplant (HCT)Review
4. Childhood HCT
5. Adult HCT
6. **Review**
7. Questions

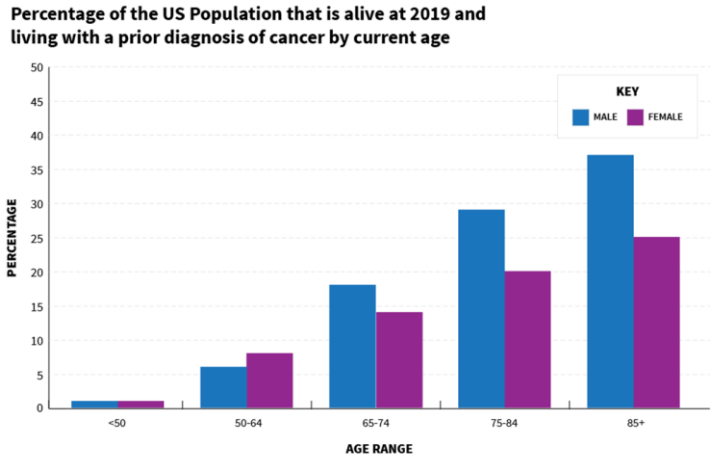
Review

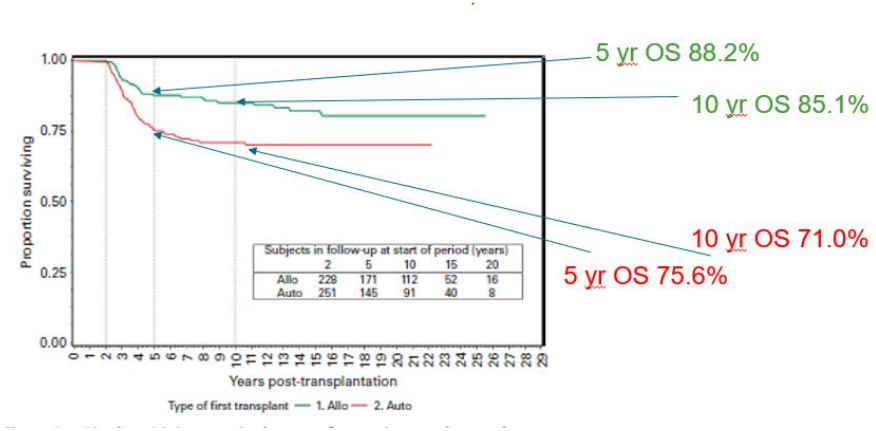
~~Cancer victim~~

cancer survivor









Thank you!
Questions

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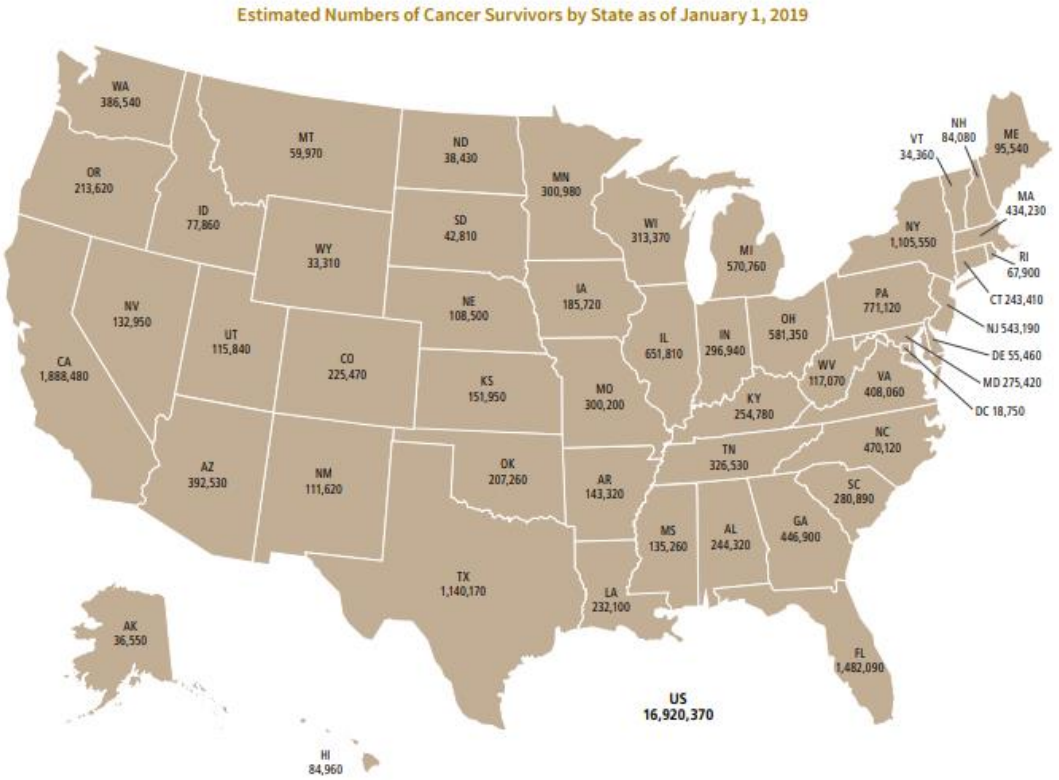
Cancer Survivorship

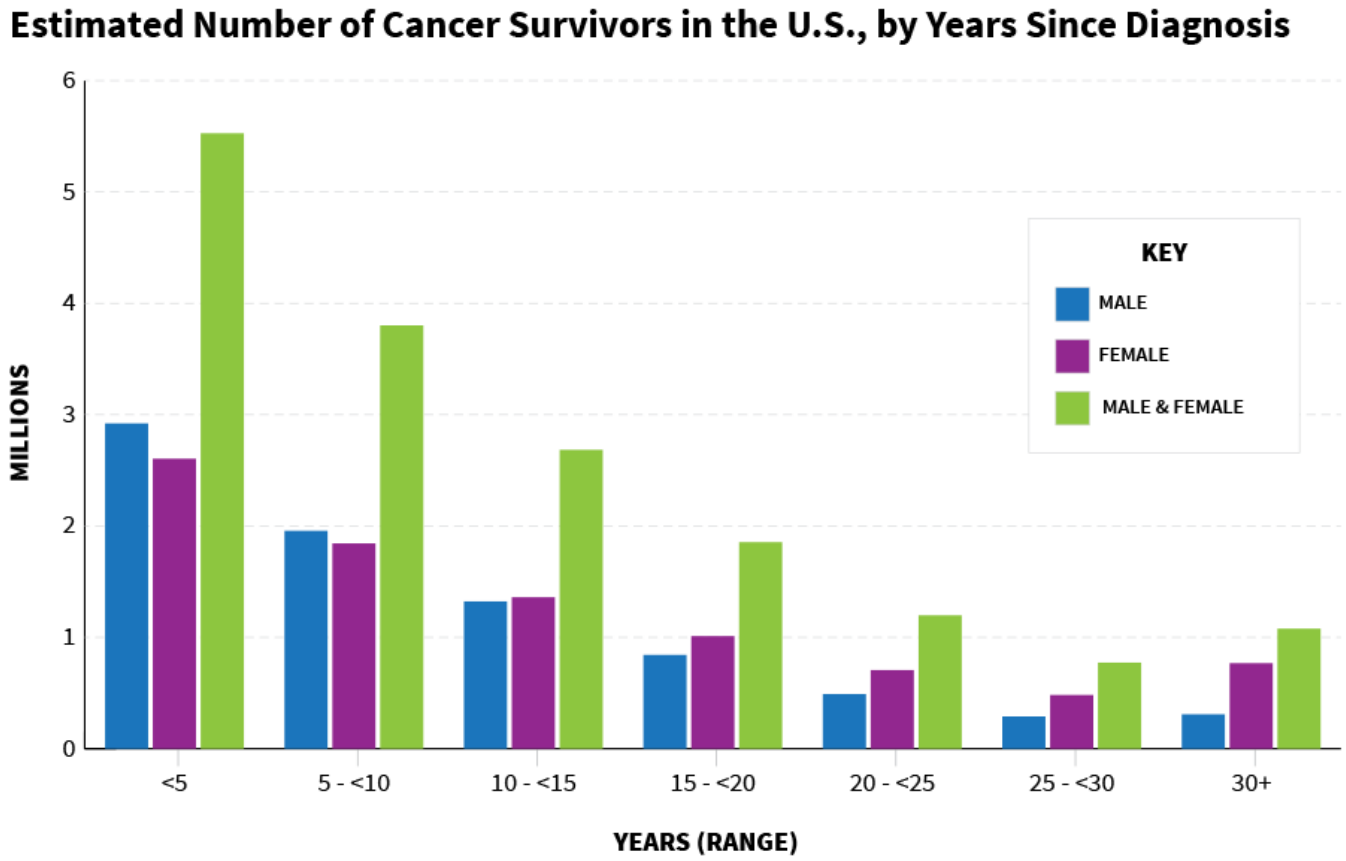
Cancer Treatment & Survivorship
Facts & Figures 2019-2021



States estimates do not sum to US total due to rounding.
Source: Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

1) https://www.cancer.org/research/cancer-facts-statistics/survivor-facts-figures.html

Cancer Survivorship



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