Pediatric Radiation Oncology

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For our children

Preface

Radiation oncology is a complex and rapidly changing medical specialty. The practicing radiation oncologist is called upon to treat tumors of many histologic types in a wide variety of anatomic locations. The emphasis of most radiation oncology practice is on the treatment of the adult patient. This is understandable since the vast majority of malignant disease occurs in the adult. The principal textbooks of radiation oncology are largely devoted to adult malignancy. There is, therefore, a need for a concise and comprehensible textbook of pediatric radiation oncology to disseminate current knowledge in the field.

The irradiation of children poses distinct problems. In many pediatric tumors the indications and techniques of irradiation are influenced by the results of complicated, multidisciplinary protocols. For many of the common malignancies of children there are ongoing new protocols for accessioning patients. The risks and complications of radiotherapy in children are of considerable consequence. New knowledge in the field is generated and reported at a rapid pace.

The practicing radiotherapist is in need of an accessible source of information and guidance in the care of young patients. Pediatric hematologist-oncologists, surgeons, neurosurgeons, neurologists, and diagnostic radiologists are, similarly, entitled to a text describing the proper use of irradiation in childhood tumors. Frequently the concerned nurse or radiation therapy technologist will also seek information on the place of radiotherapy in a child's medical management.

Pediatric Radiation Oncology is intended to serve the needs of the medical community caring for children with cancer as well as the needs of the physician in training. The authors hope that the text will contribute to an improved understanding of the benefits and risks of radiotherapy for children. It is our most earnest desire that the dissemination of knowledge about pediatric radiation oncology will improve the quality and quantity of life for children afflicted with cancer.

EDWARD C. HALPERIN, M.D.

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Finally, we acknowledge our incomparable debt to our patients. These courageous children, afflicted with cancer through no fault of their own, serve as a daily source of inspiration. If this book can partially repay our debt to them, for the privilege of being witnesses to their strength, then we shall be most grateful.

E.C.H., L.E.K., L.S.C., N.J.T.

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1

The Cancer Problem in Children

THE EXTENT OF THE PROBLEM

In the early part of the twentieth century, it was relatively unusual to observe a childhood death from cancer. The leading causes of childhood death included infectious diseases, trauma, congenital anomalies, and birth trauma. Cancer mortality per 100,000 persons in the United States and Canada from 1911 to 1916 was 3.7 for 1 to 4 year olds, 1.4 for 5 to 9 year olds, 1.3 for 10 to 14 year olds, and 2.8 for 15 to 19 year olds. Death from cancer, as a percentage of mortality from all causes, constituted only 0.43% for these same age groups. (6)

In the last part of the twentieth century, cancer in children has become a significant problem in comparison to other causes of childhood mortality. (1) Cancer is the second leading cause of death among children age 1 to 14 years in the United States. (13) There are approximately 6000 new cases of cancer annually in the United States and 2000 children die of cancer each year in this country. The age-specific incidence rates of cancer mortality in the United States are similar to those in the United Kingdom for 1978 to 1981 (Tables 1 and 2). (10)

The wide variation in childhood cancer mortality rates between nations is striking (Table 2). This variation is a reflection of genetic and environmental factors as well as the ability to ascertain and treat cases.

TABLE 1. *Age-specific cancer incidence and mortality rates per 100,000 population of the United States*

Age (Y)	Incidence	Mortality
0–4	18.1	4.3
5–9	10.1	4.6
10–14	10.5	4.0
14–19	18.4	5.2

(From ref. 12.)

TABLE 2. *Death rates per 100,000 population from malignant neoplasms: Males, age 0–4 and 5–14, 1978–1979*

	Age 0–4 (Y)		Age 5–14 (Y)
Uruguay	10.5	Costa Rica	8.9
Romania	10.3	Hungary	8.8
Greece	10.2	Portugal	8.8
Argentina	9.4	Italy	8.5
Poland	9.4	N. Ireland	8.2
Belgium	9.3	Bulgaria	8.2
Finland	9.2	Spain	7.9
Yugoslavia	8.9	Finland	7.3
Israel	8.3	Greece	7.1
Singapore	8.1	Hong Kong	6.9
Hungary	8.0		
Canada	5.6		5.7
United Kingdom			
England/Wales	6.5		6.4
N. Ireland	7.6		8.2
Scotland	5.1		4.9
United States			
White	5.3		4.8
Nonwhite	4.6		4.7

(From ref. 14.)

ANATOMIC SITES OF CHILDHOOD CANCER

The leukemias and central nervous system (CNS) tumors constitute over half of childhood tumors (Table 3). Leukemia is the most common cause of cancer mortality in children, followed by brain and CNS tumors, non-Hodgkin's lymphomas, and bone tumors (Tables 4 and 5).

THE NATURE OF CURE

The English word "cure" is derived from the Latin term *cura* and the Old French term *cure*—both meaning care. The generally accepted definition in medicine for cure is that of "successful medical treatment; the action or process of healing a wound, a disease, or a sick person; restoration to health." (5) There are several mathematical and statistical definitions of cure. Cure may be defined as that state where "the expectation of life of a group of patients free of disease become similar to that of the general population of the same sex and age constitution." (8) One way of expressing this type of probability of survival is a "relative" survival rate. The relative survival rate is the ratio of

TABLE 3. *Cancer incidence by site for children under 15, SEER Program, 1973–1976*

Rank	Site	# of Cases	% of Total	Rate per 1,000,000 children
1.	Leukemia	664	30.2	33.6
2.	Central Nervous System	409	18.6	20.7
3.	Lymphomas	298	13.6	15.1
4.	Sympathetic Nervous System	170	7.7	8.6
5.	Soft Tissue	141	6.5	7.1
6.	Kidney	135	6.1	6.8
7.	Bone	101	4.6	5.1
8.	Retinoblastoma	58	2.6	3.0
9.	Liver	26	1.2	1.3
	All Others	195	8.9	9.9
	All Sites	2,197	100.0	111.1

(From ref. 20.)

TABLE 4. *Average annual age-specific incidence rates per 100,000 population by site, 1978–1979*

	0–4 (Y)	5–9 (Y)	10–14 (Y)	14–19 (Y)
All Sites	18.1	10.1	10.5	18.4
Leukemias	6.3	3.2	2.2	2.1
Brain & CNS	3.0	2.6	2.2	1.7
Kidney & Renal Pelvis	2.0	0.6	0.2	0.1
Non-Hodgkin's Lymphomas	0.7	0.9	0.8	1.4
Hodgkin's Disease	0	0.6	1.3	3.6
Ovary	0	0.1	0.2	0.6

(From ref. 12.)

the observed percentage of survival to the percentage expected on the basis of general population experience adjusted for age, sex, race, and calendar year. Utilizing this definition, a population of patients is cured when a graph plotting relative survival rate shows a horizontal line. (10)

It is important to consider both the continuous cancer-free survival and the overall survival in the construction of survival curves. (17) Overall survival rates reflect factors other than biologic curability, including death due to complications of treatment and subjective factors such as the will of the patient to continue living with cancer or its repeated relapses, the determination of the physician to keep the patient alive, and the resources available to the physician and the patient.

The use of a semilogarithmic graph is important for assessing the possibility of cure. (17) If one observes a group of patients with a steady cancer relapse rate, then the number of patients who relapse each year declines as the number remaining in complete remission declines. If one were to plot this

TABLE 5. *The four leading causes of cancer death, United States—1985: Children under 15 years of age*

Leukemia	714
Brain and CNS	422
Non-Hodgkin's Lymphomas	102
Bone	74

(From ref. 21.)

TABLE 6. *Trends in survival by site of cancer for children under 15: 1967–73, 1974–76, and 1977–83*

Site	Relative 5-Year survival rate (percent)		
	1967–73	1974–76	1977–83
Leukemias	15	45	61
Acute Lymphocytic	18	53	68
Acute Granulocytic	0	16	26
Acute Unspecified	14	43*	42*
Brain & CNS	45	56	54
Hodgkin's Disease	78	80	88
Non-Hodgkin's Lymphomas	24	43	54
Sympathetic Nervous System	42	**	**
Soft Tissue Sarcomas	44	57	67
Rhabdomyosarcoma	34	53*	64
Kidney-Wilms' Tumor	65	74	82
Bone	28	52*	45
Osteosarcoma	26	55*	38
Ewing's Sarcoma	23	38*	46*
Retinoblastoma	82	89*	92

*Standard error of 5 to 10 percent
**No longer calculated separately
(From ref. 21.)

phenomenon on an arithmetical graph, it might appear that the risk of relapse is declining when, in truth, it is remaining constant (Figure 1). With many malignancies one can identify a poor prognosis subgroup with an anticipated early relapse as well as a better prognosis subgroup expected to have longer complete remissions. If a population of patients contains both of these groups, there will be a high relapse rate in the early years, and a lower relapse rate in latter years. An arithmetic graph of complete remission for such a population of patients suggests that the survival curve begins to form a plateau. On the other hand, a semilogarithmic graph of the same data shows the biphasic nature of the curve and the lower, but steady, relapse rate (Figure 2).

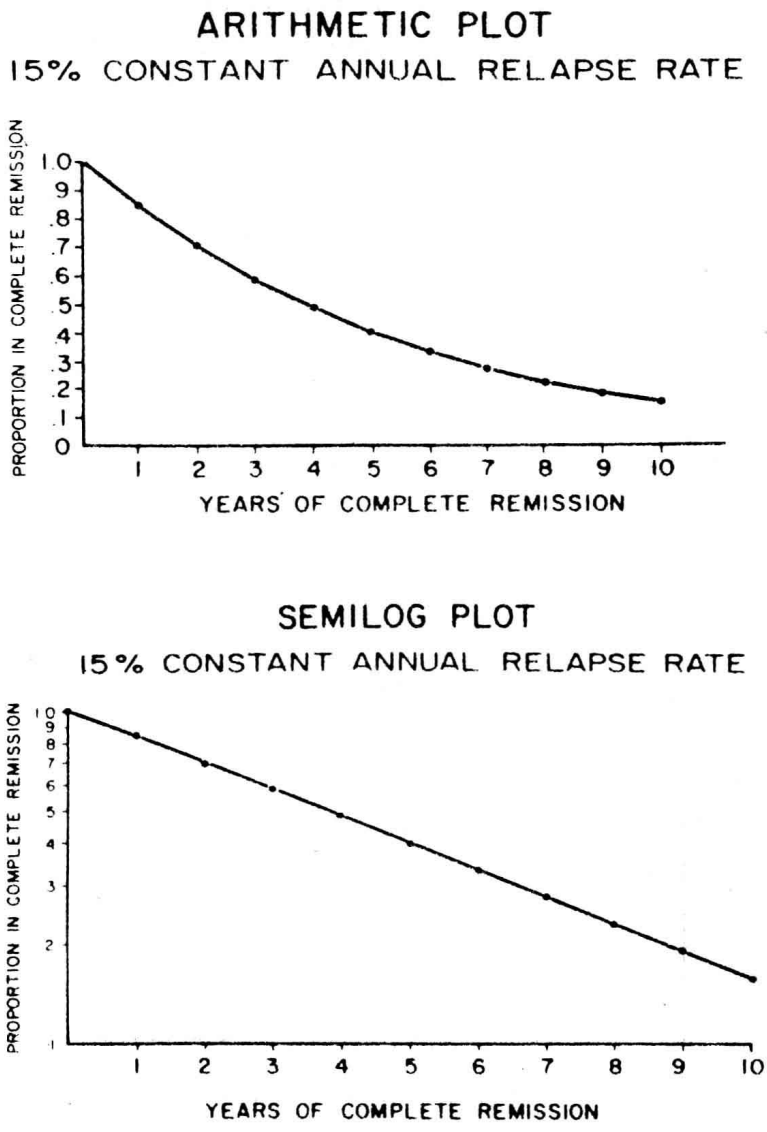
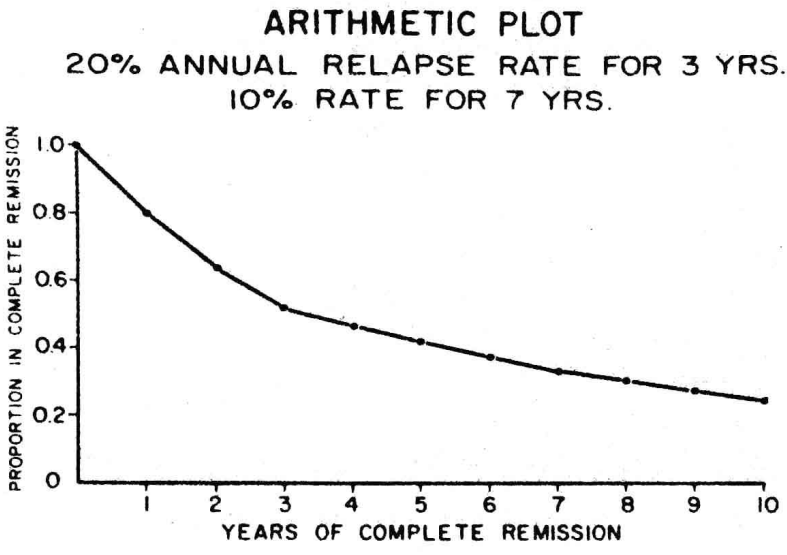


FIG. 1 The appearance of the arithmetic plot of the cancer-free survival curve, utilizing hypothetical data, implies that patients have a reduced risk of relapse after eight years. The semilogarithmetic plot of the same data, however, shows a persistent risk of relapse with no evidence of a cure (Reprinted, with permission, from ref. 17.)



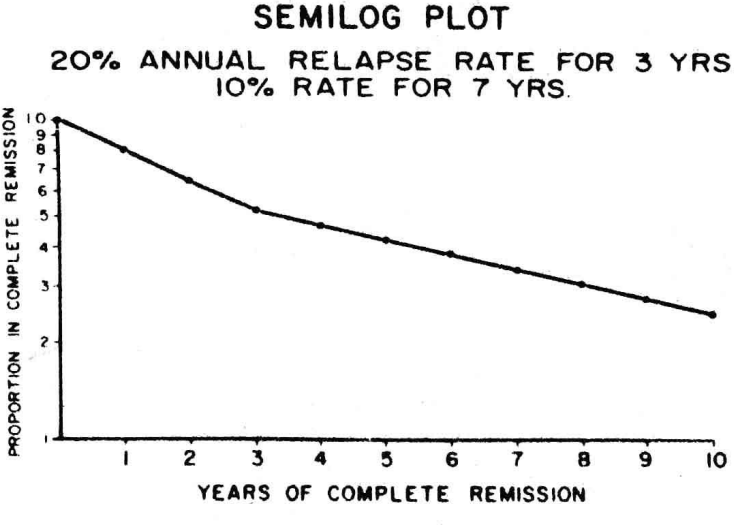


FIG. 2 When patients with good and bad prognostic features are combined, an arithmetic plot may suggest the formation of a plateau. The semilogarithmetic plot shows a biphasic curve without evidence of a cure. (Reprinted, with permission, from ref. 17.)

A frequently invoked definition of cure in pediatric oncology was initially proposed by Collins concerning Wilms' tumor.

> If one accepts the prenatal origin of this tumor as occurring within a fixed period of embryonic development, then the time of recognition and diagnosis would depend upon the rate of growth. . . .
>
> If the rate of growth was characteristic of an individual tumor, then this would govern not only the time of first appearance of the primary tumor but would also place limits upon the length of time in which a recurrence might be expected to develop. A tumor present at birth had to develop to clinically recognizable size in a period of 9 months or less. If it were to recur following surgical removal, then this should require no longer than an additional 9 months. A tumor first recognized at the age of 5 years and incompletely removed should again reach the size of clinical recognition either as a recurrence at the primary site or as a distant metastasis in a period not to exceed 5 years plus 9 months. (4)

Collins' hypothesis generally agrees with the observed rates of recurrence in embryonal cancers such as Wilms' tumor and medulloblastoma. There is not, however, biologic evidence that the "prenatal origin" of childhood tumors necessarily implies that tumor doubling times are correlated with the patient's age at the time of diagnosis.

The reported cure rates in pediatric cancer may be affected by artifacts of data acquisition and analysis. The "zero-time shift" or "lead-time bias" will extend the statistical length of survival without prolonging life. This phenomenon occurs when a new screening test or imaging study leads to the detection of heretofore unknown tumor. Even if therapy is ineffectual survival is increased by the interval provided by the earlier detection of the cancer. The "Will Rogers effect" occurs when there are improved techniques for detection of cancer metastases. This new data allows patients to migrate from lower stages of cancer to higher stages. Such migration improves survival in lower stages by eliminating those people with metastatic disease. Survival also improves in higher stages because of the addition of people with minimal metastatic disease. Survival improves in each stage while overall survival for the cancer is unaffected. This phenomenon is named after the humorist Will Rogers who is reputed to have remarked during the depression of the 1930s that "when the Okies left Oklahoma and moved to California, they raised the average intelligence in both states." (9)

With improving cure rates in childhood cancer, it is apparent that we must move beyond the statistical definition of cure and also deal with the human definition. (17) Cure must be analyzed beyond the absence of disease. It is important to provide the child with a functional cure, regaining or retaining the ability to conduct oneself in society without major handicaps or need for significant support. Planning for adequate limb function, ambulation, and activities of daily living are crucial in planning a course of treatment. Rehabilitation plays an important part of the follow up care for children with cancer. Attention to the child's emotional status is also important. By this

we mean the preservation and nurturing of a sense of well-being on the part of the child and family. Having gone through the devastating experience of cancer diagnosis and treatment, the child should be aided with coping mechanisms. The family should be given every measure of support in dealing with illness and restoration of health. The health care team should establish means to maintain an ongoing relationship with the child and family after successful treatment.

THE SITE OF CARE AND THE PEDIATRIC CANCER TEAM

The effective use of combined modality therapy has been a rewarding approach to pediatric cancer management. A coordinated group of medical and surgical specialists with expertise and interest in the clinical care of children with cancer, as well as in basic and clinical research, best directs the child's care. The complete pediatric cancer center is staffed by a pediatric medical oncologist, specially trained nurses, a pediatric diagnostic radiologist, surgeons with expertise in pediatric oncology, and skilled social workers. The group must also include a radiation oncologist committed to pediatric care. (1)

There is evidence that the diagnosis and treatment of some pediatric malignancies, particularly those dependent upon complex radiotherapy, is better conducted at university-affiliated medical centers. In an analysis of children with brain tumors, survival was compared for those children who received all or part of their treatment at university cancer centers versus those who received all or part of their treatment at community hospitals. (7) For children with medulloblastoma, the five-year survival rate was two and a half times greater for children treated at university hospitals compared to those treated at community hospitals. For brain stem gliomas there was also a greater probability of survival for those children treated at university hospitals. The five-year projected survivals for cerebellar astrocytoma, Grade I and II supratentorial astrocytoma, ependymoma, and glioblastoma multiforme (where survival is arguably less dependent upon irradiation) were similar for university-treated patients compared to community hospital-treated patients.

In another analysis, the survival of Wilms' tumor patients was compared between a county in upstate New York which contains a coordinated university and cancer center treatment program and a group of smaller counties without large treatment centers. (11) From 1950 to 1959, an era where there was relatively poor treatment for Wilms' tumor, there were no significant differences in survival between these two groups. However, from 1967 to 1972 there was a significant improvement in survival for those children treated in the county with the coordinated university and cancer center treatment program.

A recent study addressed the influence of place of treatment upon diagnosis, treatment, and survival in Wilms' tumor, rhabdomyosarcoma, and medulloblastoma in the Delaware Valley area. (13) There was an improved probabil

ity of survival in children treated at cancer centers compared to hospitals that were not cancer centers for medulloblastoma and rhabdomyosarcoma. In Wilms' tumor, however, there were not major differences in management strategy or survival between cancer centers and noncancer centers.

The available data suggests that there is a benefit to treatment at a university-based cancer center in situations where the treatment is rapidly evolving and where success requires complex treatment approaches with technically difficult surgery and/or radiotherapy. On the other hand, it appears that the site of treatment does not alter survival rates in those patients where cure may be achieved with surgical intervention alone, for tumors for which there is no significant curative treatment, and for tumors requiring multimodality therapy where the acquisition of the most up-to-date protocol information as well as the services of a consulting expert is available in the community hospital. (2,3)

CONCLUSION

The pediatric radiation oncologist can take pride in the progress being made against cancer in childhood (Table 6). All health care workers who participate in the care of children with cancer are responsible for helping to assure successful, maximally functional survival in every child with cancer.

REFERENCES

*References particularly recommended for further reading are indicated by an *.*

1. American Academy of Pediatrics. (1986): Guidelines for the pediatric cancer center and role of such centers in diagnosis and treatment. *Pediatrics* 77:916–917.
2. Begg, C. B., Zelen, M., Carbone, P. P., McFadden, E. T., Brodovsky, H., Engstrom, P., Hatfield, A., Ingle, J., Schwartz, B., Stolbach, L. (1983): Cooperative groups in community hospitals: Measurement of impact in the community hospitals. *Cancer* 52:1760–1767.
3. Cohen, M. E., Duffner, P. K., Kun, L. E., D'Souza, B. (1985). The argument for a combined cancer consortium research data base. *Cancer* 56:1897–1901.
4. Collins, V. P. (1955): Wilms' tumor: Its behavior and prognosis. *J LA State Medical Society* 107:474–480.
5. *The Compact Edition of the Oxford English Dictionary*. Oxford, Oxford University Press, 1985.
6. Dublin, L. I.: *Mortality Statistics of Insured Wage-earners and Their Families*. New York, Metropolitan Life Insurance Company, 1919.
7. Duffner, P. K., Cohen, M. E., Flannery, J. T. (1982): Referral patterns of childhood brain tumors in the state of Connecticut. *Cancer* 50:1636–1640.
8. Easson, E. C., Russell, M. H. (1963): The cure of Hodgkin's disease. *Br Med J* 1: 1704–1707.
9. Feinstein, A. R., Sasin, D. M., Wells, C. K. (1985). The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *NEJM* 312:1604–1608.
10. Frei, E., Gehan, E. A. (1971): Definition of cure for Hodgkin's disease. *Cancer Research* 31:1828–1833.