Superior Cancer Survival in Children Compared to Adults:

A Superior System of Cancer Care?

Joseph V. Simone, M.D.* and Jane Lyons, M.B.A.

Huntsman Cancer Institute

University of Utah

15 N. 2030 E., Rm 2100

Salt Lake City, Utah 84112-5330

Phone: 801-585-3880

Fax: 801-585-5886

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*To whom correspondence and reprint requests should be sent.

The last few years have seen the first overall statistical decline in U.S. cancer mortality (1,2) Though the significance of that decline is disputed (3), at least 560,000 Americans will die of cancer this year and every year for the foreseeable future. Over one-half of all cancers are diagnosed after 65 years of age and more than 99% of those dying will have developed cancer as adults (1). Thus, despite measurable improvements in survival and in the quality of survival for many patients, cancer is a growing national problem because the U.S. population is aging – one out of five Americans will be 65 or older by the year 2020 (4). It has been estimated that cancer will surpass heart disease as the leading fatal disease in the U.S. during the first decade of the new century (5).

From the beginning of the modern cancer therapy era following World War II, the courses of pediatric and adult cancers have diverged to a considerable degree. The most important difference is the progressively higher 5-year survival rate for the more common childhood cancers when compared to common adult cancers.(1) (Figs 1 & 2) In the mid-1960's, a diagnosis of childhood leukemia was a death sentence. Today, about 70% of children with acute lymphoblastic leukemia are cured. Significant improvements have been made in the outcome of other childhood cancers as well. There have been far fewer improvements in adult cancers and survival remains much the same for many patients, such as those with lung and pancreatic cancer.

These two facts – the survival divergence of adult and childhood cancer and the increasing importance of adult cancer as a public health problem – led us to examine the major differences between adult and childhood cancer to determine whether some aspects of pediatric cancer care provide a useful model for adult cancer care.

Why Is Cancer More Curable In Children?

To address this question, we have examined the relative contribution of the type of cancer, the age of the patient and structure of cancer care on the discordant outcomes. These issues are examined for the following reasons. First, adult and pediatric cancers differ substantially by phenotype and genotype. Second, adults and children differ physiologically and in the frequency of co-morbid medical conditions. Third, the cancer care delivery systems for children and adults with cancer have evolved quite differently.

Biological Differences

A striking biological difference between adult and childhood cancer is microscopic type. Virtually all adult cancers are carcinomas derived from epithelial tissue. The more common – prostate, breast, lung, colo-rectal, uterine and ovary - all arise from cells that line cavities or glands. Childhood cancers are mostly sarcomas derived from non-ectodermal embryonal tissue such as bone marrow, nerve tissue, lymph glands, bone and muscle. The five most common childhood cancers are leukemia, brain and other nervous system tumors, lymphoma, bone sarcoma and soft-tissue sarcoma.

The carcinoma vs. sarcoma and mature vs. embryonic dichotomies are so important because 40 years of experience has demonstrated that carcinomas are more resistant to radiotherapy and chemotherapy when compared to sarcomas, especially the sarcomas with embryonic features common in childhood. The reason for this difference in responsiveness is obscure. One possibility is that therapy may not only kill cancer cells of embryonic origin, but may also cause involution or maturation to a non-malignant phenotype. The frequent involution or maturation of neuroblastoma in infants (7) and the high cure rate of childhood leukemia despite evidence of persistent leukemia cells (8) support that notion. The critical importance of tumor type is underscored by the therapeutic results when patients get the “wrong” tumor type

for their age. Colon cancer, rare in children, responds to therapy the same as in the adult. Testicular cancer occurs in young adult men, but it has embryonic features and is completely curable in 80-90% of patients with modern chemotherapy.

If one compares microscopically identical cancers in adults and children, the therapeutic outcomes are often different. With modern therapy, acute lymphoblastic leukemia has a 5-year survival rate of about 75% in children. The "same" leukemia in adults has a much lower 5–year survival rate, perhaps 20-30% (9). Studies have demonstrated significant differences in the distribution of molecular, cytogenetic and immunological features of acute lymphoblastic leukemia in adults and children. For example, the Philadelphia chromosome is present in 25-30% of adults compared to less than 5% of children; this feature is associated with a very low cure rate (9).

Resilience of the Patient

Adults, especially the elderly, are not as resilient and recover more slowly from the acute toxicity of therapy or intercurrent infection. Adults are much more likely to have illnesses – diabetic, cardiac, pulmonary – which may limit therapeutic options. However, there are also major physiologic differences within the two groups: a 40-year-old vs. a 70-year-old; a 6-month-old vs. a 10-year-old. While the elderly patient is more likely to forego aggressive therapy, a fear of late sequelae may limit therapy in the growing child. However, most chemotherapeutic agents are metabolized in a similar manner, modern surgery holds few age-specific restrictions, and radiotherapy has similar dose restrictions to limit normal organ toxicity; in fact, radiotherapy is more likely to be restricted in children. Thus, patient resilience plays a role, but does not appear to be a major reason, independent of tumor biology, for differences in cure rate.

System of Cancer Care

It is axiomatic that the medical care system can have a profound influence on disease outcome. Cancer survival is worse among U.S. patients of low socio-economic status and the quality of cancer care varies widely by geography (10). It is especially true for cancer that an optimal outcome requires, from the outset, excellent coordinated care from experts in several disciplines. Unlike most other diseases, the best, and often the only, chance for cure is the first chance; an unnecessary delay, misdiagnosis, inadequate surgery or inadequate chemotherapy dosage may doom an otherwise curable patient, irrespective of the subsequent care.

The structures of cancer care for adults and children have evolved very differently in the U.S. over the past four decades. During the era – 1960 to 1990 – for which there SEER data is available, the 5-year cancer survival among children has increased 42%, from 28% to 70% (1). Cancer mortality has decreased among black as well as white children and for virtually for every cancer site, with most decreasing by at least 50%. During the same period, the 5-year cancer survival for adults increased 16.5% in whites and 13.4% in blacks. Simultaneously, two major differences in childhood cancer care evolved, advance planning of care through clinical trials and central coordination.

Participation of children with cancer in clinical trials became progressively more common beginning in the 1960's. This occurred principally at cancer centers and through national cooperative groups which evolved into today's Children's Cancer Group and Pediatric Oncology Group. A study submitted for publication by the American College of Surgeons, in cooperation with the Pediatric Oncology Group, the Children's Cancer Group and the American Cancer Society, has analyzed research protocol participation of children with cancer in the U.S. in 1992 (S. Shochat and S.B. Murphy, personal communication). In general, participation was higher for younger children, children with common cancers like leukemia and children treated at

centers participating in cooperative groups. For example, 80-90% of children 0-21 years of age with acute lymphoblastic leukemia participated in clinical trials, as did 45-57% with osteosarcoma and 70-80% with neuroblastoma. For all cancers treated at member institutions, over 60% of children participated in clinical trials. This compares to 2 or 3% of adults with cancer, though the number is higher – 5 to 20% - in some academic medical centers. For a variety of practical and philosophical reasons, oncologists are far less likely to enter adult patients in clinical trials (11). These percentages mean that 6 or 7 of every 10 children with cancer contribute in a systematic way to improving care while such information from 19 of 20 adults with cancer is simply lost.

This remarkably widespread participation by pediatric cancer patients and their physicians has had three profound effects that have distinguished pediatric from adult cancer care.

1. **Research Opportunity**. The high degree of participation in clinical trials has provided invaluable information for improving therapy and for basic cancer research. For example, much of the early work on cancer cytogenetics and molecular genetics was made possible by ready access to tissue from children participating in clinical trials, making relevant and reliable clinical correlations possible.

2. **Empirical Refinements**. The second effect was that all patients participating in a clinical trial, regardless of whether the scientific question was deep or superficial, hypothesis-driven or simply comparative, contributed invaluable information because a consistent diagnostic and therapeutic approach was agreed upon in advance and outcome data were collected systematically, pooled and analyzed by expert peers. This provided a powerful empirical engine for adjusting treatment regimens and diagnostic tools to try to squeeze a better outcome – more cures or less toxicity – from the subsequent trial. It is instructive to learn that the cure rate for

childhood acute lymphoblastic leukemia rose from about 40% in the early-1970's to about 70% in the mid-1990's *without a single new frontline therapeutic agent*. In leukemia and other cancers, improvements came largely from trial-and-error adjustments of therapeutic dosages and schedules made possible by the large pool of patients participating in clinical trials. This was true for other childhood cancers as well.

3. **Raise Community Standard**. This widespread participation in prospective, peer-reviewed treatment plans has had a profound effect on the community standard of care. Clinical trials established standards for an appropriate diagnostic workup, review of pathology, surgical approach, radiotherapy, and chemotherapy administration, as well as therapeutic efficacy and toxicity. In pediatric oncology these clinical trial standards progressively raised the community standard which benefited all patients, whether participating in clinical trials or not, since about 94% of children with cancer are treated at institutional members of a pediatric cooperative group (12).

Thus, in addition to the direct and indirect scientific benefits of the widespread participation in clinical trials, the empirical power of prospective treatment plans, systematic and uniform data collection and the progressive elevation of the community standard have contributed substantially to the dramatic improvement in survival of children with cancer.

Childhood cancer care has become centralized, with a pediatric oncologist serving as a "quarterback" of care, for several reasons. Most children are referred to experts at children's hospitals or academic health centers as soon as cancer is suspected, rather than following initial therapeutic attempts by generalists in institutions not equipped to handle all the complexities of care. The pediatric oncologist receives most of these patients and, even if the child is referred to a surgeon, becomes the coordinator of care and provider of most follow-up care. This quarterback system did not develop for adult cancer because it is far more common and most

patients are initially cared for by generalists in community hospitals. For the average adult with cancer, the various treating physicians usually see the patient in sequence with no one physician providing continuity throughout the course of the disease and with no prospective interdisciplinary plan.

Conclusion

The past thirty years has seen a far more dramatic improvement in the results of treating children with cancer than adults. Of three potential explanations for this observation, biological differences in the types of cancer with differing sensitivity to current therapeutic modalities account for most of the greater curability of childhood cancer. Although tolerance to some therapy differs by age, there is little evidence that this accounts for the general difference in cure rate observed across tumor types and ages. The long-standing participation of most children in clinical trials, an engine for empirical improvements in therapy as well as for basic and applied research, and an expert "quarterback" model of care assuring prospective multidisciplinary involvement, have contributed substantially to the better outcomes.

It is likely that adult cancer care and outcomes would measurably improve if a much higher proportion of adults participated in a peer-reviewed systematic approach to cancer care. This may be accomplished by dramatically increasing the number of adults participating in clinical trials or by the use of standard treatment guidelines and outcome measurements. Despite dogged efforts by the National Cancer Institute and academic cancer centers to increase the participation of adults with cancer in clinical trials research, the percentage has changed little over the years. The system of care for adults with cancer may largely be responsible for that difficulty. This includes factors such as widely-dispersed and highly variable cancer care providers, intellectual isolation concerning cancer, the narrow focus of a single specialty, a lack of interest in research,

the lack of an acceptable "quarterback" model for adult cancer care, economic and time pressures, and the significant clerical burden of clinical trials data management.

While efforts should continue to increase adult participation in clinical trials, one can gain the empirical advantages of systematic, prospective treatment by the complementary approach of engaging academic and community providers in an evidence-based system of "standard" care with the capture and analysis of outcome data; this is also known as disease management. Although it has its own implementation problems, disease management is being promoted in a variety of diseases to improve care and reduce costs (13,14) and has been demonstrated to influence the practice patterns of oncologists (15). A disease management system can progressively improve the quality of care, raise the community standard of care and the ability to monitor it, educate and inform physicians more effectively, reduce unjustified variability and unnecessary tests and procedures and provide easier access to clinical trials.

NCI-designated comprehensive and clinical cancer centers and other multidisciplinary care systems are developing treatment guidelines as part of their plan to provide better patient-focused care, improve communication, and improve the efficiency of their care delivery systems (16). However, most cancer patients do not obtain their care in such centers or in multidisciplinary care systems, but from a series of providers who share no plan of care. Treatment guidelines offer these patients and their community physicians a standard of care, treatment plans, outcome measures and built-in access to pertinent clinical trials.

Treatment guidelines and outcome analysis, through clinical trials or disease management, today may well be synonymous with quality cancer care. Changes in reimbursement for health care are slowly eroding the clinical research infrastructure (17) so the likelihood of financing an improved and expanded clinical trials system without government intervention is small. Thus, the need for information on the outcomes of cancer care becomes more vital to our efforts to

treat this growing health problem. Implementation of cancer disease management regionally or nationally is a formidable task, but when considered as a facet of quality care it seems reasonable, possible, prudent and in the best interests of cancer patients.

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Illustrations