

Recent advances in childhood cancer: Fifty years of progress

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ABSTRACT

Treatment of childhood cancer has been one of the biggest success stories of modern medicine. Today, upto 75% of children with access to optimal medical treatment are cured of cancer, with cure rates of some of the common cancers reaching upto 90%. This can largely be attributed to multimodality, multidisciplinary management. Childhood cancer has provided the most successful model for collaborative research integrated with clinical care and systematic application of evidence based medicine.

Depending on the type of cancer and the stage at which it is diagnosed, children may be treated with one or more modalities, including chemotherapy, radiotherapy, and surgery. Various combinations of chemotherapeutic agents have been extremely effective in inducing, consolidating, and maintaining remission. It has also facilitated limb-sparing and organ preserving surgeries for a number of cancers. Growing knowledge of the immunohistological, genetic and molecular characteristics of many types of cancer have facilitated the accurate diagnosis and stratification of patients into risk groups. As a result, children can receive individualized treatment and many low-risk patients can receive less intensive therapy, thus avoiding some of the late sequelae of intensive cytotoxic therapy, such as severe organ damage, infertility, and second malignancies.

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INTRODUCTION

The field of pediatric oncology has seen more progress than almost any other clinical area in the last Fifty years. Today, about three quarters of children diagnosed with childhood cancer can hope to achieve long-term cure (Fig. 1). Improvements in protocol-driven clinical trials and supportive care have dramatically reduced mortality rates in children and adolescents with cancer. There have been tremendous advances in the understanding of the pathogenesis, biology and treatment of pediatric cancers. In parallel, there have been major improvements in supportive care of these patients which have contributed to reduction in treatment-related morbidity and mortality.

There is a marked heterogeneity within each type of pediatric cancer and the survival rates vary depending on

the stage of the disease, age at presentation and acquired genetic abnormalities. The key to success has been the use of multimodality treatment in a multidisciplinary setting using appropriate risk stratification. The survival rates for children 0–14 years of age have increased steadily since the 1960's when the overall 5-year survival rate after a cancer diagnosis was estimated as 28%.¹ Improvements in the survival rates continued into the early 2000's in the United States with 3-year survival rates exceeding and 5-year survival rates nearing 80% for children and adolescents diagnosed during this period. These results have been possible where all there is universal access to optimal healthcare. Access to optimal care, however, continues to be an issue in the developing nations and there is an urgent need to address this. The aim of this review is to outline the newer advances in the field of pediatric oncology which

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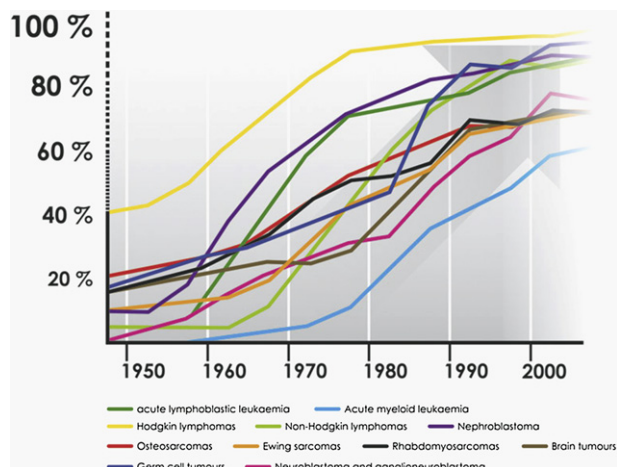


Fig. 1 Improvements in survival rates in childhood cancers over last 50 years.

have helped us in improving cure rates and reducing late effects.

RECENT ADVANCES IN CHEMOTHERAPY

For leukemias, which comprise one-third of all childhood tumors, chemotherapy has been and remains the mainstay of treatment. The successful treatment of Acute Lymphoblastic Leukemia (ALL) has provided a compelling paradigm for chemotherapeutic treatment of all cancers. Greater understanding of the biology of individual subtypes, treatment stratification and dose intensification has contributed to the dramatically improved success rates. In addition, effective chemotherapy has facilitated the avoidance of radiation in the vast majority of patients with leukemia thus sparing them a number of late effects such as poor growth, neurocognitive impairment and the possibility of a second malignancy later in life. The interesting fact is that in the last few decades, very few novel agents have been added to our armamentarium. The major successes have stemmed from better use of and combination of previously known drugs.

The striking improvement in survival rates of solid tumors over the past decades has been due to the introduction of anti-cancer drugs into regimens that previously relied only on surgery and radiotherapy for the primary tumor. The multimodality approach, which integrates surgery and radiotherapy to control local disease with chemotherapy to eradicate systemic disease, has become the standard approach to treating most childhood cancers. Specifically, the concept of **“neoadjuvant chemotherapy”** i.e., chemotherapy given prior to local treatment has

improved the success of local control dramatically and has facilitated organ preserving surgery.

The role of neoadjuvant therapy is based on outcomes of completed trials, and its use is very disease specific. The role of neoadjuvant therapy in patients with neuroblastoma was clearly outlined by a series by Rubie and colleagues who analyzed 52 patients with localized but unresectable tumors who underwent neoadjuvant chemotherapy. A response rate of more than 60% was seen and 51 of 52 children were able to undergo successful resection.² Studies have shown that there is a higher incidence of complications, including nephrectomy, in the group undergoing initial resection in contrast to those that receive neoadjuvant chemotherapy.³

Chemotherapy has been the single greatest therapeutic intervention in the treatment of bone tumors in the last four decades. Prior to its use, the mortality of bone tumors was nearly 90%. The role of neoadjuvant chemotherapy is not only in shrinking the tumor to make it more amenable for limb-salvage procedures but also for treatment of systemic micro metastasis and as a strong prognostic tool. In several other diseases like Wilms’ tumor, and hepatoblastoma the role of neoadjuvant chemotherapy has been established.

Promising results have already been demonstrated in relapsed disease using newer agents including clofarabine and nelarabine in precursor B cell and T cell ALL, respectively.^{4,5} These agents are being incorporated into frontline therapy for pediatric ALL.

RECENT ADVANCES IN RADIATION ONCOLOGY

The last two decades have seen significant technological advances for radiation delivery in terms of more precise dose delivery using newer techniques. It has moved from conventional radiotherapy using simple rectangular treatment fields to increasingly conformal radiotherapy techniques such as three dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT). The result has been improved sparing of normal tissue and, hence, the potential to improve cancer outcomes. Reducing the dose to the organs at risk using techniques such as IMRT and reducing the size of the planning target volume (PTV) using image guided radiotherapy (IGRT) enables radiation dose-escalation to be done, to improve the treatment outcomes. IMRT is an advanced approach to three-dimensional treatment planning and conformal therapy. It optimizes the delivery of irradiation to irregularly shaped volumes and has the ability to produce

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