Robert Carachi · Jay L. Grosfeld · Amir F. Azmy

The Surgery of Childhood Tumors

Robert Carachi · Jay L. Grosfeld · Amir F. Azmy (Eds.)

The Surgery of Childhood Tumors

Second Corrected and Enlarged Edition

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Robert Carachi, MD, PhD, FRCS
Professor of Surgical Paediatrics
at the University of Glasgow and Honorary Consultant
Paediatric Surgeon at the Royal Hospital for Sick Children
NHS Greater Glasgow and Clyde, Women & Children's Directorate, Yorkhill
Glasgow G3 SSJ, Scotland
UK

Jay L. Grosfeld, MD, FACS, FAAP, FRCS
Lafayette Page Professor and Chairman, Emeritus
Department of Surgery
Indiana University School of Medicine
Indianapolis, IN 46202
USA

Amir F. Azmy, MB, ChB, DS, FRCS
Consultant Paediatric Surgeon Department of Surgical Paediatrics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 SSJ, Scotland
UK

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This photograph was taken in Glasgow (March, 1998) when Professor Jay Grosfeld was awarded the Honorary Fellowship of The Royal College of Physicians and Surgeons of Glasgow. The three editors in the picture with their wives are, from left to right, Robert and Annette Carachi, Jay and Margie Grosfeld, Amir and Fatima Azmy.

This volume is dedicated to our wives,
our children, and our grandchildren.

Foreword

Surgery was at one time the only modality of treatment which was capable of curing children unfortunate enough to develop cancer. Then along came radiotherapy, chemotherapy, and now even immunotherapy; however, surgery still retains an important place and in some instances good surgery is a prerequisite for cure.

In Europe and the UK, as in the US, much of the early treatment for children with solid tumors was led by and often given by surgeons. We now, however, have multidisciplinary teams with each member having a key role to play.

Survival for childhood cancer has improved dramatically over the last 50 years and although we continue to make progress the rate of improvement has inevitably slowed down. In developed countries the major scope for improvement still lies in the organization of care. Ensuring that the pathway to diagnosis is as short as possible and ends at the team that can deliver best modern treatment, preferably in a clinical trial setting, has to be a goal for all countries. One of the biggest hurdles, however, remains getting on to that diagnostic journey in the first place and there remains a great deal to be done in education of both parents and primary care physicians to take lumps and bumps seriously. Even within Europe there are marked disparities in outcome in spite of similar treatments. Social factors and access to and compliance with care must also be considered.

The role of the surgeon is important in the direct management of children with cancer but they also play a huge supportive role. The advent of central venous lines to facilitate access for chemotherapy has revolutionized the giving of treatment. Insertion of these lines is a skilled procedure and needs to be done in a timely fashion. The oncology team surgeon usually plays this vital role.

I am delighted to see the second edition of this important book. The editors have done an excellent job in drawing together a real team of experts. This book will facilitate the education of young surgeons, keen to join the pediatric oncology team, and provide refreshment and stimulation for those already in the field.

Professor Sir Alan W. Craft

Foreword

In managing a child thought to have a malignant tumor, the day starts in the operating room, literally and figuratively. The surgeon is the key figure, whether in taking a biopsy or undertaking a major extirpation. Much depends on how that procedure is done, starting with the incision. Is it correctly placed – whether for a biopsy or a radical procedure – or will it make for problems in subsequent management? Even at this perhaps simplest of levels, it is obvious that the surgeon from the beginning plays a pivotal role in ensuring success in pediatric oncology. A trans-scrotal biopsy of a subsequently proven testicular or paratesticular malignant tumor complicates matters. How best to deal with the unnecessarily contaminated hemi-scrotal sac?

It is also inherent in the example given that modern management of the child with cancer entails working as a member of a coordinated, multimodal team. Long gone are the days when any specialist could embark on a solo course of action. The pediatric radiation therapist and chemotherapist along with the surgeon make up that team, each depending on the skill and expertise of the other.

Modern multimodal care in pediatric oncology has led to the rapid rise in survival rates of the various malignant entities to the present astonishing levels. Effective anticancer drugs have been credited with much of that progress – and rightly so. That has, however, also led in recent decades to an unfortunate undervaluation of the part surgeons have played and continue to play in contributing to that success. The surgeon's role too often is being taken for granted. It must be more appreciated and understood that the day does indeed start in the operating room. I feel this perhaps more keenly because I had the privilege of working as an intern under two great pioneering pediatric surgeons: Drs. William E. Ladd and Robert E. Gross. They were the Fathers of Pediatric Surgery in the USA, and were responsible for major steps forward in the management of children with cancer. Their surgical skills were remarkable, and made a deep impression, of course, as did their willingness to look beyond accepted techniques and methods. They were ready to explore the new and promising; Dr. Ladd, for instance trying and then advocating the transperitoneal approach to Wilms' tumors. Dr. Gross did so for routine postoperative radiation therapy for that neoplasm, thus forging the first link in the chain of interdisciplinary care. Even more memorable and important was their systematic, careful method for moving forward. Their innovations were not capricious. They came about only after careful thought, observation, and even laboratory experimentation when appropriate. Their textbooks were models of building on the logical conclusions. From the organization of those books, I first began to understand the meaning of the "scientific method."

Despite the fact that some of the best survival rates in the world resulted from what they were doing, the chemotherapist was quickly added to the radiotherapist to form the modern multimodal team. Great credit is due Drs. Ladd, Gross, and other surgeons like them, in so quickly embracing a pattern of care that was completely new, and helping to pave the path to progress.

But the day for the multimodal team nonetheless starts with the surgeon, who ideally should be a member of an experienced, interdisciplinary unit. If not, and such a well-staffed and competent pediatric cancer center is available locally, the child should be referred there. This is so because childhood cancers are very different from those that occur in the adult. Few surgeons accumulate sufficient personal experience to feel confident in undertaking the care of a child with a malignant tumor. To help them understand the intricacies of the pediatric surgical oncology, the editors have brought together in these pages the experience and expertise of an international array of surgeons and other authorities. The Table of Contents shows the wide range topics covered. They start with basic considerations such as the epidemiology of childhood tumors. The roles of associated specialties are then discussed along with a review of specific tumor types. Supportive and palliative care – extremely important topics sometimes neglected in "how to" books – are not neglected. Chapter 29 adds information concerning how best to interact with parents' groups and other psychosocial support associations. Such groups are

making their voices heard more and more, and it is appropriate and proper that they should. The surgeon must be ready to meet with such associations, to discuss their problems and to answer their questions. The second edition of this book thus brings detailed and up-to-date informing concerning what needs to be done not only before surgery, but also at the operating table and thereafter. It does more than that: It provides a blue print of how the surgeon can best fit within the modern practice of pediatric oncology.

Emeritus Professor J. Giulio D'Angio

Preface

The first edition of The Surgery of Childhood Tumors was published in 1999. The purpose of the book was to produce a comprehensive illustrated reference book on the management of childhood solid tumors focusing on those neoplasms of specific interest to pediatric surgeons. It was also intended for use by pediatricians, pediatric and adult medical oncologists, general and pediatric urologists, orthopedic surgeons, otolaryngologists and neurosurgeons. Each chapter was written by an authority in that field of pediatric oncology. Authors were selected from Europe, the United States, and Asia. Most were members of the major cancer study groups worldwide. This book was well received and the editors believed that a second edition was due because of the new important knowledge that has become available in the last few years. There have been new developments in epidemiology, tumor biology, molecular genetics of cancer, concepts of risk in relation to pediatric surgical pathology, diagnostic imaging techniques, radiation and chemotherapy. In particular, there are new surgical concepts in the evolution of minimally invasive surgery in the diagnosis and management of surgical oncology as well as the problem of vascular access provided by the surgeon and the interventionalist. Novel methods of treatment in cancer patients have advanced with the increased knowledge of the molecular biology of the cancer cell. As a consequence, the 2nd edition has had to include chapters on new therapies and technologies and up-to-date literature reviews. We trust that the readers will find these changes valuable.

We have retained our main aim in the 1st edition to have the book well illustrated with clinical images as well as detailed operative techniques and up-to-date references. The book consists of three sections:

Part A consists of eight chapters dealing with epidemiology of childhood cancer, tumor biology, and environmental carcinogens, the genetics of cancer including inherited syndromes and counseling, tumor markers and results of tumor screening programs, tumor imaging, the general pathologic principles of childhood solid tumors, and information regarding chemotherapy, radiation therapy, and immunotherapy in pediatric cancer.

Part B consists of seven chapters concerning tumors encountered in the neonatal period, and the contemporary management of Wilms' tumor and other renal neoplasms, neuroblastoma and other adrenal lesions, malignant hepatic tumors, germ cell tumors, soft tissue sarcomas, and Hodgkin's and non-Hodgkin's lymphoma.

Part C deals with some tumors managed by the specialist surgeons and other members of the cancer team and consists of fourteen chapters including chapters about malignant bone tumors, and head and neck tumors with extensive coverage of medullary thyroid cancer and multiple endocrine neoplasia syndromes. The chapter on brain tumors has been altered to include orbital and periorbital tumors. The other chapters in this section cover thoracic tumors (lung, chest wall, and mediastinum), other rare tumors observed in children, and unique aspects of reconstructive surgery following extensive procedures (limb salvage, chest wall replacement, etc.). Surgical and other complications of cancer treatment, patient and family support and counseling at diagnosis and during early postoperative care in potential survivors, palliative and terminal care, and bereavement, as well as the late effects of cancer treatment in long-term survivors are also covered in detail. This chapter also includes an extensive review on fertility in children treated for cancer. Four other new chapters have been included on minimal invasive surgery, new treatments and new strategies, central venous access and pain management. There is occasional overlap in some chapters when dealing with tumors in anatomical regions, and this was intentionally left in place and cross-referenced.

The editors wish to thank all the contributing 47 authors for taking valuable time from their busy schedules to participate in the development of this text and for submitting their manuscripts in a timely manner.

Robert Carachi
Jay L. Grosfeld
Amir F. Azmy

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Finally we would like to thank our wives and children for their continuing support and understanding while we were editing this book.

Robert Carachi
Jay L. Grosfeld
Amir F. Azmy

Contents

List of Contributors

Mr. Basith Amjad
Department of Surgical Paediatrics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Professor Richard J. Andrassy
Chairman, Department of Surgery
University of Texas Medical Center
6431 Fannin, MSB 4-020
Houston, TX 77020
USA

Emeritus Professor J. Giulio D'Angio
University of Pennsylvania Medical Center
2 Donner Building
3400 Spruce Street
Philadelphia, PA 19104-4283
USA

Dr. G. Suren Arul
Consultant Paediatric Surgeon
Department of Surgery
Birmingham Children's Hospital
Steelhouse Lane
Birmingham B4 6NH
UK

Professor Richard G. Azizkhan
Children's Hospital of Cincinnati
3333 Burnet Avenue MLC 301 8
Cincinnati, OH 45239-3039
USA

Mr. Amir F. Azmy
Department of Surgical Paediatrics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Professor Edward M. Barksdale
Children's Hospital of Pittsburgh
Department of Pediatric Surgery
3705 Fifth Avenue, Suite 4A-485
Pittsburgh, PA 15213-2583
USA

Dr. Louise E. Bath
Department of Paediatric Oncology
Royal Hospital for Sick Children
9 Sciennes Road
Edinburgh EH9 1LF, Scotland
UK

Professor Deborah F. Billmire
Riley Children's Hospital
702 Barnhill Drive, Suite 2500
Indianapolis, IN 46202
USA

Miss Elspeth Livingston Brewis
2 Grosvenor Crescent
Glasgow G12 9AE, Scotland
UK

Mr. Stephen V. Cannon
London Bone and Soft Tissue Service
Royal Orthopaedic Hospital
Stanmore
Middlesex, HA7 4LP
UK

Professor Robert Carachi
Department of Surgical Paediatrics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Mr. Paul D. Chumas
Consultant Paediatric Neurosurgeon
The General Infirmary
Leeds, LS1 3EX
West Yorkshire
UK

Professor J. Michael Connor
Duncan Guthrie Institute of Medical Genetics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Dr. Fiona Cowie
Consultant Clinical Oncologist
Beatson Oncology Centre
Western Infirmary
Durnbarton Road
Glasgow G1 1 6NT, Scotland
UK

Professor Sir Alan W. Craft
Sir James Spence Institute
Royal Victoria Infirmary
Newcastle upon Tyne NE1 4LP
UK

Dr. John Currie
Consultant Anaesthetist
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Associate Professor Andrew M. Davidoff
St. Jude Children's Research Hospital
332 N. Lauderdale-Mai1 Stop 133
Memphis, TN 38105-2794
USA

Dr. Diana L. Diesen
Duke University Medical Center
Division of Pediatric Surgery
Box 3815
Durham, NC 17710
USA

Professor Jay L. Grosfeld
Riley Children's Hospital
702 Barnhill Drive, Suite 2500
Indianapolis, IN 46202
USA

Mr. Constantinos A. Hajivassiliou
Consultant Paediatric Surgeon
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Professor Hugo A. Heij
Head of Pediatric
Surgical Centre Amsterdam
University Hospital Vrije Universiteit
De Boelelaan 11 17
P.O. Box 7057
107 MB Amsterdam
The Netherlands

Dr. Melanie Hiorns
Great Ormond Street Hospital for Children NHS Trust
Great Ormond Street
London WC1N 3JH
UK

Professor George W. Holcomb
Children's Mercy Hospital
240 1 Gillham Road
Kansas City, MO 64108
USA

Dr. Allan G. Howatson
Consultant Pathologist
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Professor Christopher J. Kelnar
Department of Paediatric Oncology
Royal Hospital for Sick Children
9 Sciennes Road
Edinburgh EH9 1LF, Scotland
UK

Mr. Charles Keys
Department of Surgical Paediatrics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Professor Jean-Martin Laberge
Montreal Children's Hospital
2300 Tupper Street C-1 137
Montreal, Quebec
H3H 1P3
Canada

Professor Michael P. LaQuaglia
Memorial Sloan-Kettering Cancer Center
Dept. of Pediatric Surgery
1275 York Avenue, Room C1 17
New York, NY 10021
USA

Dr. Dermot Murphy
Consultant Pediatric Oncologist
Schiehallion Unit
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Mrs. Marianne C. Naafs-Wilstra
Director VOKK
Scgiywstede 2d
343 1 JB Nieuwegein
The Netherlands

Emeritus Professor Jean-Bernard Otte
Cliniques Saint-Luc
Avenue Hippocrate
B- 1200 Brussels
Belgium

Dr. Susan V. Picton
Consultant Paediatric Oncologist
Department of Paediatric Oncology
Children's Day Hospital
St James' Hospital
Beckett Street
Leeds LS9 7TF
UK

Dr. Michelle Reece-Mills
Department of Paediatric Oncology
Royal Hospital for Sick Children
9 Sciennes Road
Edinburgh EH9 1LF, Scotland
UK

Professor Frederick J. Rescorla
Riley Children's Hospital
702 Barnhill Drive, Suite 2500
Indianapolis, IN 46202
USA

Dr. Milind Ronghe
Consultant Pediatric Oncologist
Schiehallion Unit
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Dr. Daniel N. Rutigliano
Memorial Sloan Kettering Cancer Center
Dept. of Surgery, Division of Pediatric Surgery
1275 York Avenue, Room H1315
New York, NY 10021
USA

Professor Robert C. Shamberger
Children's Hospital Boston
Department of Surgery
300 Longwood Avenue
Boston, MA 02115
USA

Dr. Michael A. Skinner
Duke University Medical Center
Division of Pediatric Surgery
Box 3815
Durham, NC 17710
USA

Mr. Richard D. Spicer
Consultant Paediatric Surgeon
Royal Hospital for Sick Children
St. Michaels Hill
Bristol BS2 8BJ
UK

Mr. Charles A. Stiller
Research Officer
CCRG
57 Woodstock Road
Oxford 0x2 6HJ
UK

Dr. Wendy Su
UCI Medical Center
101 The City Drive
Building 55, Room 110
Orange, CA 92828
USA

Mr. Edward S. Tobias
Duncan Guthrie Institute of Medical Genetics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Professor Benno M. Ure
Director, Kinderchirurgische Klinik
Medizinische Hochschule
30623 Hannover
Germany

Mr. Gregor Walker
Consultant Pediatric Surgeon
Department of Surgical Paediatrics
Royal Hospital for Sick Children, Yorkhill
Glasgow G3 8SJ, Scotland
UK

Dr. Hamish B. Wallace
Consultant Oncologist
Royal Hospital for Sick Children
9 Sciennes Road
Edinburgh EH9 1LF, Scotland
UK

Dr. Harry Willshaw
Consultant Ophthalmologist
Birmingham Children's Hospital NHS Trust
Steelhouse Lane
Birmingham B4 6NH
UK

Glossary of Terms

Alleles
Alternative forms of a gene or DNA sequence occuring at the same locus an homologous chromosomes.

Aneuploid
Chromosome number that is not an exact multiple of the haploid set – for example, 2n – 1 or 2n × 1.

Clone
All cells arising by mitotic division from a single original cell and having the same genetic constitution.

Diploid
Normal state of human somatic cells, containing two haploid sets of chromosomes (2n).

DNA polymerase
Enzyme concerned with synthesis of double-stranded DNA from single-stranded DNA.

Haploid
Normal state of gametes, containing one set of chromosomes (n).

Heritability
The contribution of genetic as opposed to environmental factors to phenotypic variance.

Hybridization
Process by which single strands of DNA with homologous sequence bind together.

Oncogene
Gene with potential to cause cancer.

Polymerase chain reaction (PCR)
Method of amplification of specific DNA sequences by repeated cycles of DNA synthesis to permit rapid analysis of DNA restriction fragments subsequently.

Polyploid
Chromosome numbers representing multiples of the haploid set greater than diploid – for example 3n.

Probe
Labeled DNA fragment used to detect complementary sequences in DNA sample.

Southern blotting
Process of transferring DNA fragments from agarose gel to nitrocellulose filter or nylon membrane.

Translocation
Transfer of chromosomel material between two non-homologous chromosomes.

Triploid
Cells containing three haploid sets of chromosomes (3n).

Deletion
A deletion occurs when a section of a chromosome either terminal or intestitial is lost.

Proto-oncogene
First recognized as viral oncongenes (*v-onc*) carried by RNA viruses. Subsequent ones found in the human genome are called cellular oncogenes *(c-onc*). More than 60 such proto-oncognes have been described. Their normal function is the control of cell growth and differentiation. Mutation results in appropriate expression leading to neoplasia.

Northern blotting
Blotting for analysis from RNA detects gene expression.

FISH
Fluorescent in situ hybridization. DNA probe labeled with fluorochrome and hybridized direct with a metaphase chromose spread. A fluorescent signal produced by the hybridization to the relevant chromosome is visualized using a fluorescent microscope.

Abbreviations

Organizations

CCG	Children's Cancer Group
CCLG	Children's Cancer and Leukemia Group
CESS	German Cooperative Ewing's Sarcoma Study
CLGB	Cancer and Leukemia Group B
CWS	German Cooperative Sarcoma Group
EC	European Community
ENSG	European Neuroblastoma Study Group
IACR	International Association of Cancer Registries
IARC	International Agency for Research and Cancer
ICDO	International Classification of Disease for Oncology
INSS	International Neuroblastoma Staging System
IRS	Intergroup Rhabdomyosarcoma Study Group
NCI	National Cancer Institute (USA)
NWTS	National Wilms' Tumor Study
POG	Pediatric Oncology Group (USA)
SEER (Program)	Surveillance, Epidemiology and End-Results Program
SIOP	International Society of Pediatric Oncology (Society Internationale Oncologie Pediatrique)
SWOG	Southwest Oncology Group
UKW	United Kingdom Wilms' Tumor Trials
WHO	World Health Organization

Common Abbreviations Used in the Text

ABMT	Autologous Bone Marrow Transplant
ACTH	Adrenocorticotropic Hormone
ADEPT	Antibody Directed Enzyme Prodrug Therapy
AFP	Alpha-Fetoprotein
AIDS	Acquired Immunodeficiency Syndrome
ALL	Acute Lymphoblastic Leukemia
ALL	Acute Lymphocytic Leukemia
AML	Acute Myelogenous Leukemia
ANLL	Acute Nonlymphoblastic Leukemia
APUD	Amine Precursor Uptake and Decarboxylation
ARDS	Adult Respiratory Distress Syndrome
ASR	Age Standardized Rate
ASRM	Age Standardized Mortality Rate
bFGF	Basic Fibroblast Growth Factor
BMRTC	Bone Metastasing Renal Tumor of Childhood
CFS	Congenital Fibrosarcoma
CK	Creatine Kinase
CMN	Congenital Mesoblastic Nephroma
CMV	Cytomegalovirus
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
CPDN	Cystically Partially Differentiated Nephroblastoma
CT	Computed Tomography
CUM	Cumulated Incidence Rate
DDC	DOPA Decarboxylase
DGH	dopamine β-hydroxylase
DNET	Dysembryoplastic Neuroepithelial Tumor
DOPA	3, 4-Dihydroxyphenylalanine
EBV	Epstein-Barr virus
EMG	Exomphalos, Macroglossia and Gigantism Syndrome
FAP	Familial Adenomatous Polyposis
FISH	Fluorescent In Situ Hybridization
FNA	Fine Needle Aspiration
FRC	Functional Residual Capacity
FSH	Follicle Stimulating Hormone
5-FU	5-Fluorouracil
FVC	Forced Vital Capacity
G-CSF	Granulocyte Colony Stimulating Factor
GCT	Germ Cell Tumors
GLC	Gas Liquid Chromatography
GM	Granulocyte Macrophage
HAL	Hepatic Artery Ligation
HCG	Human Chorionic Gonadotropin

HIV	Human Immunodeficiency Virus
HMMA	Hydroxymethoxymandellic Acid
HPLC	High Performance Liquid Chromatography
HSV	Herpes Simplex Virus
HVA	Homovanillic Acid
IGF	Insulin-Like Growth Factor
IR	Incidence Rate
ITP	Idiopathic Thrombocytopenic Purpura
LCH	Lens Culinaris Hemagglutinin
LDH	Lactic Dehydrogenase
LH	Luteinizing Hormone
LT	Linear Trend
Mab	Monoclonal Antibodies
MAO	Monoamine Oxidase
MDP	Methylene Diphosphonate
MDR	Multiple Drug Resistance
MEN	Multiple Endocrine Neoplasia
Mesna	2-Mercaptoethane Sulfate
MFH	Malignant Fibrous Histiocytoma
MIBG	Meta-Iodo-Benzylguanidine
MKI	Mitosis/Karryorrhexis Index
6-MP	6-Mercaptopurine
MPNST	Malignant Peripheral Nerve Sheath Tumors
MR	Mortality Rate
MRA	Magnetic Resonance Angiography
MRP	Multiple Drug Resistance Associated Protein Gene
MTC	Medullary Thyroid Carcinoma
NGF	Nerve Growth Factor
NHL	Non-Hodgkin's Lymphoma
NPY	Neuropeptide Y
NRSTS	Non-Rhabdomyosarcoma Soft Tissue Sarcomas
NSE	Neuron-Specific Enolase
OMIM	On-line Mendelian Inheritance in Man
OPSI	Overwhelming Post-Splenectomy Infection
PAS	Periodic Acid-Schiff
PCA	Patient-Controlled Analgesia
PCNA	Proliferating Cell Nuclear Antigen
PCR	Polymerase Chain Reaction
PEFR	Peak Expiratory Flow Rate
PEI	Percutaneous Ethanol Injection
PNET	Primitive Neuroectodermal Tumor
PNMT	Phenylethanolamine-N-Methyl-transferase
RMS	Rhabdomyosarcoma
SIR	Standardized Incidence Rate
SMN	Second Malignant Neoplasms
SMR	Standardized Mortality Rate
SPECT	Single Photon Emission Computed Tomography
TBI	Total Body Irradiation
TGF	Transforming Growth Factor
TLC	Total Lung Capacity
RMN	Third Malignant Neoplasms
TNM	Tumor-Node-Metastasis
TRK	Tyrosine Kinase Receptor
TS	Tuberous Sclerosis
TSH	Thyroid-Stimulating Hormone
VIP	Vasoactive Intestinal Polypeptide
VLA	Vanillactic Acid
VMA	Vanillylmandelic Acid
WAGR	Wilms' Tumor, Aniridia, Genitourinary Abnormalities (or Gonadoblastoma), Abnormalities and Mental Retardation

Acronyms of Drug Combinations

ABVD	Adriamyciri (Doxorubicin) Bleomycin, Vinblastine, Dacarbazine
Adria-VAC	Adriamycin (Doxorubicin), Vincristine, Actinomycin-D, Cyclophosphamide
BEP	Bleomycin, Etoposide, Cisplatin
BiCNU	Carmustine (Bischloroethyl-N-Nitro-surea)
CADO	Cyclophosphamide, Adriamyciri (Doxorubicin)
CCNU	Lomustine (Chloroethyl-N-Cyclohexyl-N-Nitrosurea)
Ch1VPP	Chlorambucil, Vinblastine, Procarbazine, Prednisone
COMP	Cyclophosphomide, Vincristine (Oncovin) Methotrexate, Prednisone
IVA	Ifosfamide, Vincristine, Adriamycin (Doxorubicin)
JEB	Carboplatin, Etoposide, Bleom Cin
MOPP	Mustine, Vincristine (Oncovin) Procarbazine, Prednisolone
OPEC	Vincristine (Oncovin) Cisplatin or
OJEC	Etoposide, Carboplatin
PEI	Cisplatin, Etoposide, Ifosfamide
PVB	Cisplatin, Vinblastine, Bleomycin
PLADO	Cisplatin, Adriamyciri (Doxorubicin)
VA	Vincristine, Actinomycin-D
VAC	Vincristine, Actinomycin-D, Cyclophos-phamide
VAdriaC	Vincristine, Adriamyciri (Doxorubicin), Cyclophosphamide
VIA	Vincristine, Ifosfamide, Actinomycin-D
VIE	Vincristine, Ifosfamide, Etoposide