RECENT ADVANCES IN THE MANAGEMENT OF PEDIATRIC SOLID TUMORS

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Abstract: Solid tumors make up about 30% of all pediatric cancers. The most common types of solid tumors in children include brain tumors, neuroblastoma, rhabdomyosarcoma, Wilms’ tumor and osteosarcoma. In the last decade substantial progress has been made in the treatment of pediatric solid tumors. Better understanding of the natural history of the various tumors, improved histologic classifications, new techniques to define extent of disease accurately, effective chemotherapy and improved radiation, surgical and supportive therapies have contributed to improved survival. This article reviews some of the common childhood tumors, emphasizing on current management and future directions.

Keywords: Pediatric solid tumors, Recent advances.

Survival rate for childhood cancer has improved dramatically over the last 50 years. Although we continue to make progress, there is still scope for improvement in developing countries.¹

The multidisciplinary approach to cancer treatment involving pediatric surgeons, radiation therapists and pediatric oncologists has improved the treatment and outcome of solid tumors in children.² The successful use of a combination of chemotherapeutic agents has led to the widespread use of combination chemotherapy to treat virtually all types of pediatric cancers. Since the late 1980s, neuroblastoma has been the paradigm for the use of therapies of variable intensity, depending on risk stratification determined by clinical and biologic variables, including molecular markers.³

Other advances in pediatric oncology have included the development of interdisciplinary, national cooperative clinical research groups to critically evaluate new therapies, the efficacy of dose-intensive chemotherapy programs in improving the outcome of advanced-stage solid tumors, and the supportive care necessary to make the latter approach possible. The development and application of these principles and advances have led to substantially increased survival rates for children with cancer and profound improvements in their quality of life.³

Advances in molecular genetic research have led to an increased understanding of the genetic events in the pathogenesis and progression of human malignancies, including those of childhood.³

Incidence of solid tumors in children: The annual incidence of cancer in children under 15 years of age is usually between 100 and 160 per million. There is a risk of 1 in 650 to 1 in 400 that a child will be affected during the first 15 years following birth.¹ Leukemia is the most common form of cancer in children, and brain tumor, the most common solid tumor of childhood (Table I). Lymphomas are the next most common malignancy in children, followed by neuroblastoma, soft tissue sarcomas, Wilms’ tumor, germ cell tumors, osteosarcoma and retinoblastoma.³

Recent advances in the management of pediatric solid tumors encompass diagnostic and therapeutic modalities.

### Table I. Type of cancer in childhood

<table>
<thead>
<tr>
<th>Types of cancer</th>
<th>Percentage of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>30</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>22</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>15</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>8</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>7</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>6</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>5</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>2</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>1</td>
</tr>
</tbody>
</table>

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Diagnostics comprise of molecular diagnostics, imaging techniques and newer techniques in histopathology. The newer treatment modalities are in the form of targeted chemotherapy.

**Molecular diagnostics**

Information about the human genome has led not only to an improved understanding of the molecular genetic basis of tumorigenesis but also to the development of a new discipline: the translation of these molecular events into diagnostic assays. The field of molecular diagnostics has developed from the need to identify abnormalities of gene or chromosome structure in patient tissues and as a means of supporting standard histopathologic and immunohistochemical diagnostic methods. In most instances, the result of genetic testing confirms light microscopic and immunohistochemistry-based diagnosis.

In some instances molecular analysis is required to make a definitive diagnosis (e.g. primitive small round cell tumor, poorly differentiated synovial sarcoma and lipoblastic tumor).

The molecular genetic methods most commonly used to analyze tumor material include, direct metaphase cytogenetics or karyotyping, fluorescent in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR).

Additional methods such as comparative genomic hybridization, loss of heterozygosity analysis and complementary DNA (cDNA) microarray analysis may eventually become part of the routine diagnostic repertoire but are currently used as research tools at referral centers and academic institutions.

The value of molecular genetic analysis of patient tissue is not limited to aiding histopathologic diagnosis. Many of the most important markers provide prognostic information as well. For example, MYCN amplification in neuroblastomas,^4^ is strongly associated with biologically aggressive behavior. Amplification of this gene can be detected by routine metaphase cytogenetics or by FISH and current neuroblastoma protocols include the presence or absence of MYCN amplification in their stratification schema.

New technologies are emerging that permit accurate, high-throughput analysis or ‘profiling’ of tumor tissue: gene expression can be analyzed by using RNA microarrays and proteins by using proteomics. These approaches identify a unique ‘fingerprint’ of a given tumor that can provide diagnostic or prognostic information. Proteomic analysis can also identify unique proteins in patients’ serum or urine; such a profile can be used for early tumor detection, to distinguish risk categories and to monitor for recurrence.

Once the quality and consistency of sample material can be refined and data management and statistical analyses validated and standardized, gene profiling microarrays will probably be used routinely to analyze pediatric malignancies.

**Imaging techniques**

**CT scan/MRI**

Although CT is well established, it utilizes ionizing radiation and therefore modern imaging of most tumors in the pediatric population should preferentially be performed by MRI where this is feasible. Furthermore, MRI has advanced so rapidly in recent years that it is now considered the superior modality (outside the lungs) irrespective of the radiation issues surrounding CT. However, CT is generally more readily available, cheaper, and easier for the patient than MRI and new scanners are now so fast that patients who previously required a general anesthetic for CT may now be able to have the scan performed under sedation or even unsedated. CT provides excellent images of lung parenchyma, mediastinum, head and neck, abdomen and pelvis. Intravenous injection of contrast medium is essential to delineate mediastinal masses, hepatic tumors, renal masses and head and neck tumors and can provide superior vessel details by CT angiography compared to conventional angiography (Fig.1). Spiral CT rotates the X-ray beam and the diametrically opposing detectors around the patient. Modern scanners have multiple detectors (typically 64 or 128) with the capability of very thin slice thicknesses (as low as 0.625 mm) allowing very rapid scanning of large body areas that can be completed in 5–10 sec which, with extensive image post processing and manipulation, can finally produce reconstructed planar and 3D images.

![Fig.1. CT scan with contrast showing the relationship of tumor to great vessels of a superior mediastinal tumor](image-url)
Magnetic resonance imaging (MRI) provides exquisite anatomical detail of many pediatric tumors. It has advantages over CT and US scanning including greater inherent tissue contrast, multiplanar imaging and non-invasive angiography and avoids exposure to ionizing radiation.

New super-fast sequences and improving scanner design (i.e., ‘open-MR’) is transforming the feasibility of MRI in the pediatric age group. MRI should be considered the imaging modality of choice for tumors of the musculoskeletal system, central nervous system, including the spine, head and neck tumors, as well as the abdomen, pelvis and mediastinum. Modern sequences and the use of contrast agents can also give information about the vascularity and enhancement characteristics of tumors. This can also be of benefit in the assessment of vascular malformations. Magnetic resonance angiography (MRA) is particularly useful in evaluating tumor proximity or involvement of major vessels. Whole-body MR may also compete with positron emission tomography (PET) imaging to stage abdominal tumors. Specific advantages of MR include determination of resectability of hepatic tumors using combined MR and MRA; staging of neuroblastoma in the bone marrow, lymph nodes, liver and spinal canal; response of bilateral Wilms’ tumor and nephroblastomatosis; and detection of pelvic tumors with sagittal sections, and peritoneal tumors with contrast enhancement.

Fast spin-echo short inversion time inversion-recovery (STIR) whole-body (MR) imaging is an evolving technique that allows imaging of the entire body over a reasonable period of time. Its wide availability and lack of radiation exposure makes this method appealing in children. Bone marrow lesions, including marrow infiltration from lymphoma, metastases and tumor-related edema, are observed with high signal intensity and are more easily detected on STIR images than with scintigraphy. Focal parenchymal lesions can be distinguished by their slightly different signal intensity, but pathologic lymph nodes cannot at present be differentiated from normal nodes on the basis of signal intensity. The STIR technique is highly sensitive for detection of pathologic lesions, but it is not specific for malignancy; thus, the method cannot be used to differentiate benign conditions from malignant neoplastic lesions with certainty at present.

**Nuclear imaging**

Nuclear scintigraphy is useful in diagnosis, staging, and assessment of tumor response and evaluation of treatment in various pediatric tumors. The technological aspects of radioisotope scanning are particularly important when imaging children.

Image magnification and single photon emission computed tomography (SPECT) are essential to state-of-the-art pediatric nuclear medicine. Multiple head detector gamma camera systems are available and have the advantages of increased resolution and sensitivity and decreased time of examination in a child.

Nuclear imaging techniques such as bone scans, meta-iodo-benzyl guanidine (MIBG) scans, and Indium111-diethylenetriaminepentaacetic acid (DTPA) octreotide scans have greatly increased the sensitivity and specificity of both diagnostic and follow-up protocols for pediatric solid tumors. Molecular targets that are specific for certain pediatric tumors are now being developed. Targets include cell membrane receptors targeted by specific ligands (such as octreotide), subcellular organelles targeted by false transmitters (such as MIBG) and cellular proteins targeted by antibodies.

**Positron emission tomography**

Positron emission tomography (PET) involves the acquisition of physiologic images based on the detection of radiation from the emission of positrons. Positrons are emitted from a radioactive substance fluorodeoxyglucose (FDG) administered to the patient. Different color intensities on a PET image represent different levels of tissue glucose metabolism. Healthy tissue accumulates some of the tagged glucose, which shows up on the PET images. However, cancers, which use more glucose than normal tissue, accumulate more of the substance and appear brighter than normal tissue on the PET images (Fig. 2).

Fig. 2. PET scan showing the various color coding to differentiate between normal and cancer cells depending on the uptake of tagged glucose.
PET scans are useful both in the detection of cancer and in examining the effects of cancer treatment by characterizing biochemical changes in the cancer. PET may be combined with CT to exactly localize areas of abnormal tissue, both for biopsy and to plan surgery. PET scans are now being used more widely in the pediatric population although usually only in specialized cancer centers.

**Biopsy**

The importance of biopsy techniques has increased as the use of preoperative chemotherapy has become common for many childhood cancers. In the past, definitive diagnosis was made at the time of surgical resection of the primary tumor. Currently, many children undergo percutaneous or open incisional biopsy rather than initial resection. Moreover, with a better understanding of the molecular changes associated with these malignancies, definitive diagnosis and accurate staging can be accomplished with smaller specimens. This should lead to less morbidity associated with the diagnosis of solid malignancies in children.

There has been a progression towards less invasive techniques to obtain a diagnosis, from complete surgical extirpation to incisional biopsy to percutaneous needle biopsy and minimal-access surgery. This change in practice has been driven not only by the evolution of surgical technique but also by an improved understanding of the molecular markers used for both diagnosis and risk stratification in pediatric solid malignancies.

The types of specimens which might be submitted to the pathologist are cytology specimen, needle biopsy, incisional biopsy, excisional biopsy and resected specimen.

Fine needle aspiration cytology (FNAC) is used less frequently in children. The recent application of molecular techniques and electron microscopy to supplement light microscopy has increased the histio-type specificity of FNAC and may lead to its increased application in pediatric solid malignancies.

Percutaneous needle biopsies may be performed by palpation in the extremities and other superficial locations, such as lymph nodes. Deeper biopsies require either ultrasonography or computed tomography (CT) guidance.

Minimal access surgery: The widespread use of minimal-access surgery, including laparoscopy and thoracoscopy, has had a significant impact on general pediatric surgery over the last 25 years. The application of both laparoscopy and thoracoscopy has now grown to include the initial diagnosis of childhood malignancies and the assessment of refractory and metastatic disease. Diagnostic laparoscopy and biopsy have been used in several settings in the management of children with solid malignancies. Biopsies obtained using laparoscopic techniques have a high rate of success in yielding diagnostic tissue. Laparoscopy allows the surgeon to obtain larger tissue samples than may be obtained with core needle biopsy. This is particularly relevant if larger samples are required for biologic studies. In the initial diagnosis, laparoscopy aids in identifying the site of origin of large abdominal masses. Laparoscopy is superior to CT in assessing intraperitoneal neoplasms and for the evaluation of ascites. Thoracoscopy is frequently used to evaluate metastases either at the time of initial diagnosis or after follow-up imaging. Mediastinal lesions can also be biopsied or resected using thoracoscopy.

**Immunohistochemistry**

The introduction of immunohistochemistry to the armamentarium of diagnostic histopathology has revolutionized the subject and has significantly contributed to the management of pediatric neoplasia. In recent years there has been a massive expansion in the use of antibodies in tissue diagnosis. Immunohistochemistry is based on the technique that a particular component of a tissue, acting as an antigen, can be identified by a specific antibody carrying a label which can be rendered visible (Fig.3).

Fig.3. Immunohistochemistry of rhabdomyosarcoma showing positivity for desmin

Two types of antibodies are used. The first are polyclonal and tend to be less specific and sensitive while the second, which are now more commonly used, are monoclonal antibodies which allow for the use of very sensitive and highly specific detection techniques. Example panels of some antibodies commonly used in the diagnosis of pediatric tumors are provided in Table II.
Flow cytometry

In the case of neoplasia, the features which are most usefully measured using flow cytometry are ploidy and cell surface marker phenotype. Neoplasms can be either diploid, i.e., with a normal DNA content or aneuploid, i.e., those which have other than a normal content. Aneuploidy usually correlates with tumor aggressiveness and a worse prognosis; however, in neuroblastoma hyperdiploid tumors have a better prognosis.11

Chemotherapy to targeted therapy

The prognosis for malignant solid tumors has improved since the introduction of effective chemotherapy capable of reducing the tumor volume and making previously unresectable tumors resectable. The operation also becomes safer and easier after pre-operative chemotherapy. Furthermore, there is no delay in treating metastatic disease, which is detectable at diagnosis in a significant proportion of patients.

Staging: Once the diagnosis has been confirmed, the extent of the tumor (size, position, relationship to surrounding structures, appearance of lymph nodes) must be established. Though there is no single uniform staging approach for childhood malignancies, the physician will need to be aware

Table II. Antibodies useful in pediatric tumor diagnosis

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antisera/ Cell lineage marked</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45 Leukocyte common antigen</td>
<td>Leukocytes</td>
<td>Lymphomas</td>
</tr>
<tr>
<td>CD20 (L26)</td>
<td>B lymphocytes</td>
<td>Lymphomas</td>
</tr>
<tr>
<td>CD45RO(UCHL-1)</td>
<td>T lymphocytes</td>
<td>Lymphomas</td>
</tr>
<tr>
<td>CD30 (Ber H-2)</td>
<td>Activated lymphocytes/macrophages/ Reed-Sternberg cells</td>
<td>Hodgkin’s disease/Anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>CD15 (LeuM1)</td>
<td>Reed-Sternberg cells</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>CD68 (KP1)</td>
<td>Macrophages</td>
<td>Histiocytic neoplasms</td>
</tr>
<tr>
<td>Kappa/Lambda</td>
<td>Ig light chains</td>
<td>Lymphoid clonal proliferation</td>
</tr>
<tr>
<td>Neuron-specific enolase (NSE)</td>
<td>Neuroectoderm</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>S100</td>
<td>Glial/Schwann cells/others</td>
<td>Neurofibroma, etc., Langerhans cells</td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td>β2-microglobulin</td>
<td>PNET</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Neuroectoderm/neuroendocrine</td>
<td>Ewing’s/PNET</td>
</tr>
<tr>
<td>MIC-2 (CD99)</td>
<td>MIC-2 gene product (glycoprotein P30/32)</td>
<td>Ewing’s/PNET</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Intermediate filaments/mesenchyme</td>
<td>Ewing’s/soft tissue sarcoma</td>
</tr>
<tr>
<td>Actin (common, smooth muscle, sarcomeric)</td>
<td>Muscle filaments</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Desmin</td>
<td>Muscle (smooth/ striated)</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Striated muscle</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Myo D-1</td>
<td>Skeletal muscle</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Cytokeratins (AE1-AE3, CAM 5.2, etc.)</td>
<td>Epithelial</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>CD1a</td>
<td>Langerhans cells</td>
<td>Langerhans cell histiocytosis</td>
</tr>
</tbody>
</table>
of various investigations for staging of each tumor type according to the current protocols (Table III).

Increasingly, the chemotherapy response of the primary tumor in the post-surgical specimen is used in deciding post-operative treatment for a number of malignant solid tumors.

The effective use of cancer chemotherapy requires a thorough understanding of principles of neoplastic cell growth kinetics, basic pharmacologic mechanisms of drug action and pharmacokinetic and pharmacodynamic variability. The most common anticancer drugs are cytotoxic agents which are cell poisons that act indiscriminately on most cells, either causing direct damage to DNA or inhibiting cell replication. Cancer chemotherapy relies on exploiting the therapeutic index - the ratio of cell killing in the malignant cell population compared with killing of normal cells.

Multiagent therapy has three important theoretical advantages over single-agent therapy. Firstly, it maximizes the cell kill, while minimizing host toxicities by using agents with non-overlapping dose-limiting toxicities. Secondly, it may increase the range of drug activity against tumor cells with endogenous resistance to specific types of therapy. Finally, it may also prevent or slow the development of newly resistant tumor cells.

**Adjuvant chemotherapy**

Adjuvant chemotherapy is used after all of the known and visible cancer has been removed surgically or with radiation and should be given as soon as possible after definitive local therapy. A delay to allow for recovery from surgery or radiation therapy may compromise the chance of curing the patient. The aim is to prevent metastatic recurrence by eliminating micrometastatic tumor deposits in the lungs, bone, bone marrow, or other sites. It has been demonstrated to be efficacious for most of the common pediatric cancers, including Wilms’ tumor, Ewing’s sarcoma, osteosarcoma and rhabdomyosarcoma.

Increasingly, chemotherapy is used in a neo-adjuvant setting (before the definitive treatment) in pediatric solid tumors as chemotherapy shrinks the tumor and the operation becomes safer and easier. Neoadjuvant chemotherapy also provides earlier set treatment for micrometastases. The drive for all new therapies is to devise compounds that maximally target the tumor, avoiding systemic side effects.

**Monoclonal antibody therapy**

The era of monoclonal therapy has firmly arrived. Rituximab, a monoclonal antibody targeting cells expressing CD20 antigens, is licensed for use against follicular lymphoma and diffuse large B-cell non-Hodgkin’s lymphoma (NHL). Cetuximab is active against tumors expressing epidermal growth factor (EGFR). It has been used in adult practice against metastatic colorectal cancer and advanced squamous cell cancer in the head and neck.

### Table III. Investigations for staging of pediatric tumors

<table>
<thead>
<tr>
<th>Germ cell</th>
<th>Wilms’ Neuroblastoma</th>
<th>Lymphoma</th>
<th>Rhabdomyosarcoma</th>
<th>Hepatoblastoma</th>
<th>Osteosarcoma</th>
<th>Ewing’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP level</td>
<td>USS Abdo CT/MRI Abdo</td>
<td>Urinary Catecholamines</td>
<td>Bone marrow aspirate and trephine</td>
<td>CT/MRI scan local tumor</td>
<td>CT/MRI liver and abdo</td>
<td>MRI (or primary) before biopsy</td>
</tr>
<tr>
<td>HCG</td>
<td>Chest X-ray; CT chest</td>
<td>Bone marrow aspirate/ trephine</td>
<td>CSF exam</td>
<td>CT chest; MRI abdo/ pelvis</td>
<td>MR angio-graphy; CT chest</td>
<td>CT chest</td>
</tr>
<tr>
<td>MRI/CT; Abdo/chest</td>
<td>Bone/ MIBG scan; CT chest/ MRI abdo; Estimation of N-myc copy; +1p deletion from fresh tumor</td>
<td>CT chest; MRI of abdo/pelvis; bone scan</td>
<td>CT/MRI brain scan (for head/neck disease); Bone scan; Bone marrow; aspirate/ trephine</td>
<td>Bone marrow; aspirate/ trephine</td>
<td>Bone scan</td>
<td>Bone scan; bone marrow; aspirate/ trephine; fresh tumor for chromo- some analysis</td>
</tr>
</tbody>
</table>
Target therapy

Tyrosine kinase inhibitors act on genes that are responsible for many aspects of cell survival. These genes are important in cellular proliferation, differentiation, motility, and apoptosis. Other targets that may be inhibited by small molecules include endothelial and vascular endothelial growth factors (EGF/VEGF) and once again evidence of expression has been found in cell lines in many pediatric tumors. Drugs targeting these pathways are currently undergoing phase I and II trials in the pediatric setting.

Cancer vaccination and T-cell therapy

Vaccination works by stimulating host T-cells to fight off disease. Anticancer vaccines have been worked on for many years and recent increased understanding of cellular biology has meant there have been crucial developments in producing useful anticancer vaccines. Vaccination strategy is not only dependent on optimizing antigen presentation but also the interaction of that presenting cell with disease-modulating T-cells. The most exciting results have been seen using patient-specific vaccines derived from autologous tumor cell lines. Melanoma, which increasingly affects teenagers and young adults, has shown the most susceptibility to a vaccination approach. A recent report of patient-specific dendritic cell vaccines in a cohort of heavily pretreated patients with metastatic disease, will hopefully prove to be a large step forward in the long search for a successful anticancer vaccine.14

Surgical procedures in pediatric cancer care

Primary surgical resection: In many cases of solid tumors, surgical excision of primary tumor is the preferred local treatment since radiotherapy has a much greater risk of long-term sequelae. The general principles of choice of local treatment are that surgical excision is the treatment of choice where: (i) complete excision is possible and results in improved survival and cure; (ii) it will give functional and cosmetic results better than those obtained by other treatment.

Central venous catheters and implantable devices: Insertion of central venous catheter is probably the single most frequent operation that pediatric surgeons perform while caring for a child with malignancy. Centrally placed, long-term venous catheters are used for the administration of chemotherapy, antibiotics, and for blood sampling. Central venous catheters make care easier, both for the child and for the medical team. Currently there are two main types of catheters used in clinical practice—tunnelled, external catheters (Hickman®, Broviac®, Groshong®) and totally implanted access devices such as a portocath. External, tunnel catheters are generally easier to access, are less expensive than portocaths, offer less risk of extravasation into sub-cutaneous tissue, allow more rapid infusions, and can be removed easily at the end of treatment. However, the portocath offers an improved cosmetic result, less restriction in normal activities, less maintenance care and they are well protected, thus decreasing the chance of damage, and are associated with a lower risk of infection (Fig.4).

Feeding gastrostomy: Clinical experience has demonstrated that gastrostomy tubes are an effective way to deliver medications and to provide nutrition to children experiencing excessive emesis. Providing nutrition through a gastrostomy tube alleviates the frustration associated with forced feeding of the child via the mouth. Maintenance of normal patient nutrition throughout cancer treatment allows normal growth and improves quality of life.

Oncological complications: Surgeons may also be consulted to deal with complications related to other forms of treatment: extravasation of chemotherapy agents causing tissue necrosis, typhlitis (neutropenic enterocolitis), intestinal perforation, strictures or avascular necrosis, or other damage due to late effects of radiotherapy.

Surgical decisions, as well as those concerning chemotherapy, radiotherapy, and overall treatment strategies are best made after joint discussion, which is facilitated by a formal system of consultations such as regular multidisciplinary oncology team meetings (Tumor board), as well as maintaining communication between the key team members during the treatment.

Future directions

The result of the advances in knowledge of pediatric cancer is the need for all specialists to work together in an organized and coherent team approach. With increased...
survival rates for childhood cancer, philosophy of treatment has changed over the years from ‘Cure at any cost’ to ‘Cure at least possible cost’.

Surgeons, physicians and pathologists have a responsibility to ensure the supply and retention of tumor and normal tissue samples for research purposes if progress in diagnosis, prognostication and treatment is to be maintained. The application of RT-PCR and the generation of tissue microarrays is a revolution in cancer research with massive potential for early therapeutic gain. The role of diagnostic histopathology in the management of pediatric neoplasia is greater today than ever. The constant desire to improve survival with highly toxic therapies has led to a demand for a more detailed assessment of individual neoplasms in terms of specific histological types and their variants, stage and histological grade. The remarkable and rapidly accruing insights into the molecular biology and cytogenetics of tumors and tumorigenesis has not reduced the role of pathology. Rather it has imposed a need for pathologists to do more with tumor samples submitted for examination.

So what does the future hold? It is likely that gross disease will continue to be debulked by traditional treatment modalities. This may be followed by establishing a patient-specific, molecular tumor profile with microarray technology, allowing a targeted attack of disease residuum with small molecules, immunomodulation or vaccination.

**Points to Remember**

- **Improved understanding of the molecular genetic basis of tumorigenesis has translated into diagnostic assays to identify abnormalities of gene or chromosome structure in patient tissues and as a means of supporting standard histopathologic and immunohistochemical diagnostic methods.**
- **Advances in imaging have helped in better diagnosis and prognostication of pediatric solid tumors.**
- **Targeted chemotherapy including monoclonal antibodies and adjuvant chemotherapy has revolutionized the treatment.**
- **Advent of central venous lines to administer chemotherapy has made care of the child easier.**

**References**