

Pediatric surgical oncology in China: present and future

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Pediatric surgical oncology is a relatively new and rapidly developing field. Over the past 50 years, great progress has been made in diagnosis, treatment, and survival of children with cancer. In the 1960s, the survival rate for children with malignant solid tumors was below 25%, whereas it has exceeded 75% at present. This dramatic change is attributable to the creation of multidisciplinary therapy, the improvement of surgical techniques, the successful use of chemotherapy, the application of radiation therapy and the progress in understanding of tumor molecular biology.^[1] The progress in the treatment of solid tumors in children can be reviewed in the following aspects.

Improvement of surgical techniques

Surgery is the mainstay of treatment for all benign and malignant solid tumors. Within the multidisciplinary treatment team, the surgeon plays a critical role in the diagnosis, staging, and therapy. Surgical management has evolved from an aggressive en bloc resection at diagnosis to a more tailored approach, with resection for low stage tumors at diagnosis and biopsy with neo-adjuvant chemotherapy for advanced stage tumors. Nephron-sparing surgery is the treatment of choice for children with bilateral Wilms' tumor (WT), or WT in a single kidney, or WT and a disease of the contralateral kidney, or benign kidney tumor.^[2] Improvement of surgical techniques, anesthetic monitoring, and postoperative management has also significantly reduced the morbidity and mortality associated with resection of the tumors. The pediatric surgical oncologist must have a good collaboration with all those involved in the care of the patient and participate

in multidisciplinary tumor board discussions to determine the optimal surgical care for the patient.^[3]

Surgical technique requirements are different in children of different ages, and many techniques are special in tumor surgery. In China, many children with tumors are operated on by general pediatric surgeons who have less professional training on tumor surgery. There are higher risks for intra-operative bleeding and spreading. Therefore, the qualification and up-grade of surgical techniques in pediatric oncologic surgery in China are crucial.

The use of minimally-invasive surgery (MIS) techniques in children is growing with the availability of smaller instruments and equipment more suitable to the patient. MIS, including laparoscopy, retroperitoneoscopy and thoracoscopy, can be used for diagnosis (biopsy) and treatment (resection) in various malignant solid tumors in children, such as resection of ovarian tumor, adrenal tumor, retroperitoneal tumor and intrathoracic masses.^[4] Potential advantages of MIS techniques include a decreased parietal trauma (cosmetic benefit, bowel adhesions) and less postoperative discomfort (postoperative pain, analgesics requirement, postoperative ileus, and length of hospital stay). The disadvantage of laparoscopic surgery is the loss of tactile sense and quick finger pressing is required to stop unexpected sudden bleeding. A new design of scope-using instrument, the "artificial finger-tip" might be considered to help control sudden bleeding in combination with a thermometer, a manometer, and a fine ultrasonic probe. To explore a new instrument, of course, is the job of engineers, but they need information from the surgeons as well.

New technologies are constantly emerging. Gamma Knife surgery has been used to manage pediatric cerebral tumors and arteriovenous malformations.^[5,6] High-intensity focused ultrasound (HIFU) ablation has been used to treat liver tumors.^[7,8] However, surgical excision is still the fundamental technique for solid tumors and will continue to play an important role in the multidisciplinary treatment of solid tumors in children. As the complexity of therapy increases, pediatric surgeons are imperative to be familiar with new radiation therapy techniques, new chemotherapeutic agents, and the progress that is being made in immunodiagnosis, immunotherapy, and molecular biology.

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doi:10.1007/s12519-009-0018-1

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Progress of chemotherapy

Chemotherapy is now an integral part of nearly all cancer treatment regimens.^[9] Adjuvant chemotherapy refers to the use of chemotherapy for systemic treatment following surgical resection of a clinically localized primary tumor. The goal is to eliminate the disease that is not detectable by standard investigative means at or beyond the primary tumor's site. Neoadjuvant chemotherapy refers to chemotherapy delivered before surgery in an effort to increase the rate of total tumor removal and treat micrometastatic disease as early as possible.

Combination chemotherapy refers to the use of multiple agents, which have different mechanisms of action and non-overlapping toxicities, and provide synergistic antitumor activity with minimal side effects. The importance of multi-agent combination chemotherapy has been clearly demonstrated in children with malignant solid tumors over many years. In the recent years, chemotherapy regimens have been sequentially modified to reduce toxicity while maintaining survival. Improved prognosis has been seen in patients with pre-operative chemotherapy for advanced stage tumors.

Role of radiation therapy in pediatric cancer

Radiation therapy for the management of pediatric cancer is most frequently combined with surgery and chemotherapy as part of a multidisciplinary treatment plan. The sensitive nature of pediatric tumors requires the use of a combined therapy approach to maximize tumor control while minimizing the long-term side effects of treatment.

Postoperative radiation is the most common adjuvant treatment of tumor. A postoperative approach allows a review of histologic studies of the complete tumor specimen, including identification of the tumor margins. The radiation dose can be more accurately tailored to the pathologic findings after tumor resection.

Molecular genetic research on pediatric malignancies

The explosion of 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 diagnostic assays. The results of genetic testing are helpful to confirm light microscopy and immunohistochemistry based diagnosis. In some instances, e.g., small round cell tumor, poorly differentiated sarcoma, molecular analysis is required to make a definitive diagnosis.^[10]

Molecular genetic analysis of the patient tissue not only aids histopathologic diagnosis, but also many of the important markers provide prognostic information as well. For example, *MYCN* amplification in neuroblastomas is strongly associated with biologically aggressive behavior. Current neuroblastoma protocols include the presence or absence of *MYCN* amplification in their stratification schema.

Risk stratification in treatment of pediatric tumors

As more information is available about diagnostically and prognostically useful genetic markers, therapeutic strategies will change accordingly. With molecular profiling, patients can be categorized to receive a particular treatment on the basis of not only the tumor's histopathologic and staging characteristics but also its genetic composition. Some patients whose tumors show a more aggressive biologic profile may require dose intensification to increase the chances of survival, otherwise the patients may benefit from a less intensive therapy. Such an approach may allow the maintenance of high survival rates while minimizing long-term complications of therapy.^[11]

The paradigm for the use of different therapeutic intensities on the basis of risk stratification drives the management of neuroblastoma. Current studies of the treatment are based on risk groups. The most important clinical variables appear to be age and stage at diagnosis, and the most powerful biologic factors appear to be *MYCN* status, ploidy, and histopathologic classification. Patients with low-risk disease are treated with surgery alone, whereas those at high risk are treated with intensive multimodality therapy that includes multi-agent, dose-intensive chemotherapy, radiation therapy, and stem cell transplantation.^[12]

Targeted therapy

Another major change in the treatment of cancer has been the concept of targeted therapy. As the molecular bases for the phenotypes of specific malignancies are being elucidated, potential new targets for therapy are becoming defined. Information about the molecular profile of a tumor type can be assembled from a variety of emerging methods, including immunohistochemistry, FISH, RT-PCR, cDNA microarray analysis, and proteomics. This information can be used to develop new drugs designed to counter the molecular abnormalities of neoplastic cells. For example, blocking oncogene function or resoring suppressor gene activity may provide tumor-specific

therapy. In addition, molecular profiling may lead to the development of drugs designed to induce differentiation of tumor cells, block dysregulated growth pathways, or reactivate silenced apoptotic pathways.^[1]

Inhibition of angiogenesis

Although remarkable progress has been made in the past years in the treatment of childhood malignancies, not all types of cancer have enjoyed this improvement in prognosis. Thus, clinical trials are ongoing in which novel treatment approaches are being evaluated, including immunotherapy, radionuclide therapy, and the use of agents that induce tumor apoptosis or differentiation. In addition, treatment strategies such as the use of angiogenesis inhibitors are needed. Angiogenesis is the biologic process of new blood vessel formation. Besides as part of several normal physiologic processes, angiogenesis is an essential pathologic condition of cancer. Compelling data suggest that inhibition of angiogenesis can not only prevent tumor-associated neovascularization but also affect tumor growth and spread.^[13]

Evolution of postoperative nursing

Conventional routine nursing after an abdominal operation includes four main items: lying in bed; nothing by mouth; gastric decompression; and continuous intravenous drip combined with, particularly for children, immobilization of the extremities. Those are so divergent from children's willing, i.e., seeing mother, no pain, free moving, and tasteful eating. A major abdominal operation disturbs the abdomen, causing intestinal paralysis, and fasting and gastric decompression are often required. For kids with nasal tube and continuous intravenous drip, immobilization of the extremities is also reasonable. Crying of a baby is said to be good for expansion of the lungs, beneficial to prevent pneumonia. For one hundred years, this traditional pattern of abdominal nursing has been naturally accepted in all hospitals around the world.

It is happy to see children with abdominal tumor removed by laparoscopy with a minimal trauma and no big abdominal wound. It makes the mother able to hold the baby out and feed with sips of fluid at times. For those with severe abdominal reaction, a mobile gastric suction apparatus and small local immobilization can be applied. It may allow the mother to feed sips of water, which can be sucked out by the gastric drainage. In critical cases, mentally blurred, the patient should be confined to bed. Even though, it is advisable to put the

baby under "sleeping therapy", with positive pressure oxygen ventilation 2-3 times everyday for expansion of the lungs. That may lessen mental and physical strain of the mother and the baby.^[14]

Everybody with normal sensation will be certainly against pain. Postoperative analgesia should never be neglected.^[15] But surgeons are rarely aware of the pain induced by postoperative physical examination, such as changing dressing and removing stitches. Application of topical anesthetic adhesives before injections would be welcomed by the child and the mother. I saw some nurses who applied the anesthetic adhesive tapes to both the baby and the mother at the same time and the same site, and the puncture was held until the mother felt no pain. Thus, even though the baby still cried during puncture, the mother believed no pain. In the new era of humanistic medicine, those kinds of old traditional coercive savage treatment without reasonable explanation would be appealed even sued to the court.

Perspectives of pediatric surgical oncology in China

Although tremendous progress in the treatment of pediatric cancer has been made in China, there are still gaps compared with the advanced international level.

The future perspectives of pediatric surgical oncology in China is to establish nationwide cooperative research groups for the investigation of various pediatric solid tumors. In that way, sufficient number of patients could be gathered to study the nature and clinical characteristics of various malignant tumors, and make randomized trials possible of comparative treatment regimens and patients stratified following stipulated risk criteria.

The pediatric surgical oncologist must have a good collaboration with all those involved in the care of the patient and participate in multidisciplinary board discussions to determine the optimal surgical care for the patient. In addition, the qualified pediatric surgical oncologist should be familiar with the surgical principles for the peculiarities of tumors and current treatment protocols. The improvement of pediatric tumor surgery in further exploration and the improvement of surgical skills will improve the survival and long-term life quality of the patients.

Funding: None.

Ethical approval: Not needed.

Competing interest: None.

Contributors: Zhang JZ is the single author of the paper.

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Received June 5, 2008

Accepted after revision October 7, 2008

Correction

In *World Journal of Pediatrics* 2009; 5(1) Page 51: Titus A Ogunlesi should have been Tinuade A Ogunlesi in the byline, and the affiliation should be Olabisi Onabanjo University not Adebisi Onabanjo University.