Development of Pediatric Oncology

Dušanka Dobanovački[1], Radoica Jokić[1], Božica Vujošević[2], Anđelka Slavković[3]

SUMMARY

The first publication about surgical treatment of tumors in children in medical literature dates from the beginning of the 19th century. Operations were a method of choice to treat. New development in science such as microscopy research, anesthesia, antisepsis, X-ray, and radium therapy has changed the approach to malignant diseases. The remarkable achievements in survival of oncology patients today are the results of a multimodal, multi-institutional, and multidisciplinary collaboration. Pediatric oncology differs from the oncology for adult patients in the type, generic considerations, diagnostics, and treatment approach. Many pediatric subspecialties are required to evaluate, treat, and manage children with malignant diseases, including provision of primary modalities and multiple supportive care services.

KEY WORDS: *History of Medicine; History, 19th Century; History, 20th Century; Medical Oncology; Pediatrics*

Arch Oncol 2010;18(4):132-5.
UDC: 616-006:616-053.2:94
DOI: 10.2298/AOO1004132D

[1]Institute for Children and Adolescents Health Care of Vojvodina – Pediatric Surgery Clinic Novi Sad, Serbia; [2]Oncology Institute of Vojvodina – Department of Radiotherapy Sremska Kamenica, Serbia, [3]Clinical Center – Pediatric Surgery Clinic Niš, Serbia

Correspondence to:
Prof. Dušanka Dobanovački, Institute for Children and Adolescents Health Care of Vojvodina – Pediatric Surgery Clinic Novi Sad, Serbia
dodob@yahoo.com

Received: 24.05.2010
Accepted: 26.05.2010

The ancient Egyptians mentioned both benign and malignant tumors and tried to cure them, but surgical treatment really started at the time of Galen. Although *cancer* means crab in Latin, this term actually generated from Hippocrates who gave the name *karkinoma* to a group of diseases including cancer of the breast, uterus, stomach, and skin. Much later, the recommendation for surgery and complete removal of tumors dated from the time of Renaissance and famous French surgeon Ambroise Pare (1).

The early oncologic records date from the 18th century. The specialized study of the cancer started and hospitals specialized in cancer treatment were established. New development in science such as microscopy research, anesthesia, antisepsis, X-ray, and radium therapy has changed the approach to malignant diseases.

Until the 18th century, the tumor morbidity and mortality in children and adolescents were unknown or were involved into the health problem of overall population. Whether the appearance of a tumor was sporadic or it was unrecognized is a still an unanswered question.

PAST OF PEDIATRIC ONCOLOGY

Nephroblastoma

In 1814, Rance published an article describing renal tumors in children (2). Sixty years later, Eberth (3) wrote a publication about tumor with classic pathologic description, which is today known as nephroblastoma tumor. Not many years after, Conheim (4) published a similar description of a tumor, called a congenital sarcoma of the kidney. In 1979, William Osler recognized that many descriptions made by other authors and tumors called by different names as embryonal sarcoma, sarcoma of the kidney, adenomyosarcoma, and sarcoma muscular were nephroblastoma of the kidney (5).

In 1899, Max Wilms published his master thesis about renal tumors and reviewed the literature (6). Classic description of nephroblastoma accepted the eponym Wilms' tumor after him.

Mr. Jessop at the Leeds Infirmary performed the first nephrectomy in children in 1877 (7). Excision was the only tumor treatment until 1915. Friedlander of Cincinnati applied radiation therapy in 1916 (8). Operative mortality was high, and the early healing results in children were only 5% to 6%. Ladd standardized the surgical technique and, by reducing operative mortality, increased the survival rate to 20% (9).

In 1954, actinomycin-D became the first effective chemotherapeutic agent for treatment of Wilms' tumor (10). In 1963, Sutow and colleagues showed the effectiveness of vincristine in disseminated Wilms' tumor (11). Farber and his group recorded in 1966 a 2-year survival rate of 81% with combination of excision, postoperative irradiation, and actinomycin-D (10). The era of combination therapy started.

As the time passed, there were numerous reports about malignancies in childhood, but no institution registered a large series of tumors. In 1969, the collaboration in gathering statistically significant number of patients started, and three cooperative groups – the Children's Cancer Study Group (CCCSG), the Cancer and Acute Leukemia Group B (CALGB), and the Southwest Oncology Group (SWOG) – combined to form the National Wilms' Tumor Study Group (NWTS). At that time, the protocols of therapy were established (12). Further clinical researching and better knowledge on pathology, diagnostics, and optimal treatment of pediatric malignancies has initiated the founding of The International Society of Pediatric Oncology (SIOP). The clinical protocols conducted by SIOP differed from the NWTGS in that that the therapy was given before surgery. The results were that patients with preoperative treatment demonstrated the significant improvement: in 1971, the First SIOP study showed that preoperative radiotherapy may prevent tumor ruptures during surgery and may induce a favorable stage distribution. Such coordinated treatment efforts subsequently led to more SIOP studies (nine studies up to now) and protocols, and substantially increased survival in many children with cancer. Study SIOP 95 treatment involves many other tumors with the aim to prevent the rupture of the tumor and to increase the survival rate (13).

Teratoma

The cuneiform tablets of the Chaldeans of about 2000 B.C. describe a child with a problem that could be a sacrococcygeal teratoma (14). However, the first exact description of this tumor in infant dated from Saxtoph and Duvigneaut in 1790 (15).

In 1841, Stanley described the appearance of sacrococcygeal teratoma in several patients and reported the first successful excision of such a tumor. The operations were performed by Blizard (16). In 1869, Rudolf Virchow, professor of pathology at the University of Berlin, presented a lecture entitled *About the Sacrococcygeal Growth of the Schiewenian*

Child to the Berlin Medical Society (17). He suggested that the anatomical composition of these sacrococcygeal tumors was so diverse that classification was not possible and that in that time commonly used term *cystosarcoma* was inappropriate. As a part of description of the diverse gross anatomy, he stated, "One can find in different parts of tumors a further development into formations which not only correspond with different tissues of the body but at times with whole regions of it, forms of which I have called *teratomas*. As an example, in certain areas the forms of a pelvis with muscle masses attached, nerves and a completely developed foot protrude from this rather rudimentary mass" (17).

Virchow's description of anatomical structures of some sacrococcygeal tumors was the starting point for the classification of this heterogeneous group of benign and malignant tumors called teratomas. The etymologic study of the word teratoma showed that it comes from Classical Greek and means "monstrous tumor" (*teratos* (monster) and *oncoma* (a swelling)). The term teratoma is widely accepted and used despite it originates from a gross description, which defines neither histological tissue, nor it describes physiologic significance or prognosis (18).

Teratomas have been observed in aborted fetuses in the past. Some research resulted from experimental studying of mice and rats. Thus, the relationship between alpha-fetoprotein, yolk sac carcinoma, and some type of malignant teratoma was noticed by Duval, 1891 (19) and confirmed by Teilum in 1959 (20). The modern view on the etiology of this tumor postulated Steinmann in his PhD thesis in 1905 (21).

Complete surgical removal has been a treatment of choice after the diagnosis since the first decades of the 20th century (22). As tumor derived from germ cells, it manifested in wide types and commonly used classification was established in 1982 by Gonzales-Crussi containing also a grading system (23).

Teratomas are relatively easy to resect from surrounding tissues. Chemotherapy followed the surgery for malignant teratomas. Sometimes preoperative chemotherapy was applied for surgically inaccessible locations. Last decades of the 20th century were marked by increased use of fetal-maternal ultrasonography and it made possible prenatal diagnosis and early postnatal treatment of these tumors.

At present

Pediatric malignancies are distinguished from adult malignancies in type, prognosis, and distribution of the tumor. Statistical data show two peaks in this population: in early childhood and adolescence. During the first year of life, embryonal tumors (neuroblastoma, Wilms', rhabdomyosarcoma, etc.) are the most common ones. As children grow, an increased incidence of bone malignancies, and gonadal germ cells malignancies (testicular and ovarian carcinomas) is noticed, mostly after puberty (24).

Pediatric oncology is different from oncology in adults also in generic considerations, diagnostics, and treatment approach. Development of malignant diseases in children is close to development of the normal tissue – in adults, malignancy generates from present tissue. There is an important role of genetic factors in baseline of malignancies in children (13).

The first feature that characterized pediatric oncology is congenital origin of malignant diseases. It is believed that some malignant diseases present gestational defects in tissue development and differentiation. For example, neuroblastomas do not have the analogous tumor in adults. Their tissue is similar to fetal adrenal medullar tissue. Thus, neuroblastoma *in situ* and spontaneous regression of neuroblastoma is two courses of the same process – delayed development of tissue maturation (25, 26).

The next issue in pediatric oncology is that sometimes it is not possible to distinguish benign from malignant diseases (27). Special methods like staining procedures, immunocytochemistry, and measurement of biofunctional expression of antibodies are used. In addition, protein detection in relation to DNA Western blotting and correlation to imunohistochemical results has to be used.

Pathologists make the diagnosis, grade the local statement of the tumor in accordance with the TNM classification, and determine the risk of tumor as low, medium or high (28, 29). According to tumor histology findings, different protocols are used. All solid tumors in children require tissue diagnosis; therefore, biopsy of the suspected neoplasm is necessary. Staging with sentinel node biopsies has become a standard of care for several malignancies.

The treatment for childhood malignant diseases is presented into multidisciplinary programs. At present, four major disciplines are clinically involved: surgery, radiotherapy, chemotherapy, and immunotherapy (30). Before the beginning of treatment, a plan for total care needs to be formulated by interdisciplinary consultation. Surgery, radiotherapy, and chemotherapy are the main steps towards satisfactory and definitive healing. The first two have a limited approach because they are used to treat a localized disease. In most malignancies, microscopic metastases are disseminated when the patient is diagnosed and chemotherapy is necessary to complete the treatment. Combined modality therapy has been responsible for the improvement of survival rates in children with cancer. Modern management entails the coordinated use of surgery, radiation therapy, and chemotherapy, usually with more than one drug.

The strategy for the application of chemotherapy must be individualized for each patient. Chemotherapy is useful in following circumstances: (a) preoperative application with or without radiotherapy to make easier the removal of the large tumors or to avoid mutilative operative procedures; (b) application together with radiotherapy for tumors at the surgically inaccessible localization, administration with radiotherapy to treat metastases or micrometastases; and (c) in cases with disseminated disease as a palliation treatment. The chemotherapeutic agents may produce acute or chronic complications and must be used with considerable caution. Attention has to be paid because many of them are immunosuppressive. Chemotherapy usually presents a combination of drugs, such as VAC (vincristine, doxorubicin or dactinomycin, and cyclophosphamide) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Combination therapy is a standard method because combination of drugs has a different mechanism of action and non-overlapping toxicities. Once again, it is necessary to emphasize that prior the administration of chemotherapy, a biopsy of the suspected neoplasm and a sentinel node is obligatory.

Radiation therapy can be used to treat the tumor, prevent the spreading of metastases or to relieve the pain. Radiation therapy uses photons, electrons, and protons. In pediatrics, treatment of tumors with conformal three-dimensional radiation therapy and proton radiation therapy significantly reduces potential damage to surrounding healthy tissue.

A general principle of radiation therapy is to destroy malignant cells while not damaging the normal ones. The therapeutic ratio is defined as the dose required for destruction of cancer cells, divided by the dose tolerated by normal tissue (31). Normal cells differ in their radiosensitivity; the more active division of the cells is and the more immature they are, the more sensitive they are to radiation damage. Cells within the hair follicle and the bone marrow are examples of those sensitivities. In children, many tissues are dividing and maturing and the therapeutic ratio tends to be narrow in the young. Irradiation may damage the growth and development of a skeleton; it may impair organ functioning (liver, kidney, or lung), gonadal effects (hormonal functioning) and in addition it can cause infertility and genetic damages (31). This is why gonads must always be protected against ionizing rays. For CT and MRI where the visualization of slices in sequences is important, sedation of children younger than five is necessary.

Radiotherapy is rarely used in children, who are more susceptible to adverse delayed effects of ionizing radiation than the adults are. With more focused beams, such as conformal radiotherapy and better sedation and immobilization techniques, radiotherapy is becoming more frequently applied in children. Acute adverse effects from radiotherapy are less severe than from chemotherapy and depend entirely on which part of the body is irradiated and the means of administration (impaired growth resulting from cranial or vertebral irradiation, endocrine dysfunction from midbrain irradiation, pulmonary or cardiac insufficiency from chest irradiation, strictures, and adhesions from abdominal irradiation, and infertility from pelvic irradiation).

Adverse treatment effects that occur early in therapy include metabolic disorders, bone marrow suppression, and immunosuppression and the risk of life–threatening infections. Adequate pain management is very important. The World Health Organization (WHO) guidelines are useful in the management of pain associated with cancer and cancer therapy. At all stages of caring for children with cancer, principles of palliative care should be applied to relieve pain and suffering and to provide comfort (13). Ionizing radiation such as x rays is recognized as carcinogenic. Long periods, from 5 to 10 years, are well-known periods of oncogenesis for second malignant neoplasms in irradiated sites. A careful follow-up of all long-term survivors of radiation therapy is necessary. It is well known that development of secondary leukemia can be a long-time effect after an aggressive chemotherapy for colonic carcinoma (32).

Prognosis in children with Wilms' tumor who are younger than 6 months is better and therapy is less aggressive. Mesoblastic nephroma can be found in a newborn as a benign tumor. In children younger than 6 months, nephrectomy is enough for satisfactory results but after the age of 12 months, a careful follow-up is necessary.

The main reason for great morbidity and mortality in children with malignant diseases are infections. They could arise because of defects in defensive processes (B and T cell-immunity, splenectomy) by malignancies itself, or as a consequence after chemotherapy and radiotherapy. An active or passive immunization is necessary.

Recent research tried to describe the quality of life and to evaluate mental problems and neurological damage in patients with malignant diseases. A scoring system was applied in order to measure the quality of life. According to Karnofsky performance status scale, pediatric Lansky play performance scale was established to estimate the functional status among the pediatric oncology patients. This scale was used by parents who scored their children's activities, the children being at the age between one and sixteen (33-35).

The practice of multimodal therapy, chemotherapy combined with surgery and radiotherapy, are essential in oncology. In some malignancies, biochemotherapeutic type of treatment is performed with interferon (alpha, beta, gamma), interleukin-2, or erythropoietin.

It is a rule that all patients with cancer should be referred to an appropriate specialized center as soon as possible when the diagnosis of cancer is suspected. Treatment of children with cancer is one of the most complex practices in pediatrics. It begins with a requirement for the correct diagnosis, accurate staging of the extent of disease, provides appropriate multidisciplinary and usually multimodal therapy, and evaluates the possibilities of recurrent disease and of adverse late effects of the disease. Throughout the treatment, every child with cancer should have the benefit of the expertise of specialized teams of providers of pediatric cancer care, including pediatric oncologists, pathologists, radiologists, surgeons, radiotherapists, nurses, and various support staff including nutritionists, social workers, psychologists, pharmacists, and other medical specialists (36).

Clinical care for a child diagnosed with cancer involves a multidisciplinary approach and includes a coordinated team comprised of a specialist in pediatric oncology, pediatric radiation oncology (stereotactic radiosurgery, stereotactic radiation therapy, and intensity modulated radiation therapy), and pediatric surgery. Radiation oncologists work with clinical physicists to bring the latest technological developments from industry to patients' treatment plans, which are created by using the most advanced computing and imaging techniques.

Modern trends in pediatric oncology

At the beginning of the 21st century, malignant neoplasms remain the second death cause among children from 1 to 12 years old in the United States (24). There are some improvements in treatment: in 1974, five-year survival for children with malignant diseases was 56% while in 2000 it was 75%. Most pediatric patients survive their disease and associated treatment but the long-term consequences of therapy and the late adverse effects are now a point of interests in clinical researches.

Today, great improvement occurred in all fields directly connected with oncologic diseases. One of them is better understanding of the molecular base of the disease. It is known that the childhood neoplasms are arising from disorders of genetic processes involved in control of cellular growth and development. A number of genetic conditions are associated with risks for childhood cancer like neurofibromatosis type 1 and 2, Down syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis, Von Hippel-Lindau diseases, xerodermia pigmentosum, ataxia-telangiectasia, nevus basal cell carcinoma syndrome, and Li-Fraumeni (P53) syndrome (37).

Cancer is known as a complex disease arising from alterations that occur in a wide variety. Alteration in normal cellular processes such as signal transduction cell cycle control, DNA repair, cellular growth and differentiation, translational regulation, senescence, and apoptosis can result in occurrence of a malignancy. Two major classes of genes have

been implicated in the development of cancer: oncogenes and tumor suppressor genes (37).

Development of malignant diseases in children is close to development of the normal tissue – in adults malignancy generates from presented tissue. There is an important role of genetic factors in baseline of malignancies in children. Mutation of p53 suppressor gene is mentioned in development of some malignancy (13, 38). The first genetic abnormality that occurs in a malignant disease is the presence of the minute chromosome named a Philadelphia chromosome (Ph +) (39).

Recent research in Wilms' tumor pathology documented that there are more congenital genetic defects in chromosomes 11 on 11p13 or 11p15 (40).

The use of genetic engineering helps researchers to identify oncogenes and proto-oncogenes. These data about congenital basis of malignancy in children point out that ontogenesis and oncogenesis are more similar than different processes.

Nowadays, research tries to explain the interactions between genetic characteristics and the environment as a potential factor. In environmental studies, but without any convincing evidence, it is suspected that the non-ionizing power frequency electromagnetic fields, pesticides, parental occupational chemical exposures, dietary factors, and environmental cigarette smoke may be the cause for occurrence of malignancies.

Perhaps this is the question for future researches: how to engage the human immune system to use body's own defenses against the malignant diseases.

Conflict of interest

We declare no conflicts of interest.

REFERENCES

1 Cancer Chemotherapy – A Timeline. Magic Bullets. Chemistry vs. Cancer. Available from: http://www.chemheritage.org/educationalservices/pharm/chemo/re

2 Rance TF. Case of fungus haematodes of the kidney. *Med Phys J*. 1814;32:19.

3 Eberth CJ. Myoma sarcomatoides renum. *Virchow's Arch Pathol Anat Physiol*. 1872;518.

4 Cohnheim J. Congenitales, guergestreiftes Muskelsarkom der Nieren. *Virchow's Arch Pathol Anat Physiol*. 1875;64.

5 Osler W. Two cases of striated myo-sarcoma of the kidney. *J Anat Physiol*. 1879;14:229.

6 Wilms M. Die Mischgeschwulste der Niere. In: von Arthur Georgy, editor. Leipzig; 1899. p. 1-90.

7 Annotations: Extirpation of the kidney. *Lancet*. 1877;1:889.

8 Friedlander A. Sarcoma of the kidney treated by the roentgen ray. *Am J Dis Child*. 1916;12:328.

9 Lad WE. Embryoma of the kidney (Wilms' tumor). *Ann Surg*. 1938;108:885.

10 Farber S, Toch R, Sears EM. Advances in chemotherapy of cancer in man. In: Greenstein JP, Haddow A, editors. Advances in Cancer Research. Vol 4. New York: Academic Press; 1956. p. 1-71.

11 Sutow WW, Thurman WG, Windmiller J. Vincristine (leurocristine) sulphate in treatment of children with metastatic Wilms' tumor. *Pediatrics*. 1963;32:88.

12 Othersen HB Jr. Wilms Tumor (Nephroblastoma). Ch 34. In: Welch KJ, Randolph JG, Ravitch MM, et al., editors. Pediatric Surgery, 4th ed. Chicago: Year Book Medical Publishers, Inc.; 1986. p. 239-302.

13 Cvetkovic P. Clinical Pediatric Oncology. Belgrade: Sava Centar; 2000. (In Serbian).

14 Balantyne JW. Teratologie. London: Williams and Nougate; 1894.

15 Svesko H. Teratoma regionis coccygealis. *Gynaecology*. 1953;135:153.

16 Stanley E. On congenital tumours of the pelvis. *Med Chirurg Trans*. 1841;24:231-4.

17 Virchow R. Ueber Die Sakralgeschwulst Des Schliewener Kindes. *Klin Wschr*. 1869;46:132.

18 Woolley MM. Teratoma. Ch 31. In: Welch KJ, et al, editors. Pediatric Surgery, Vol 1. 4th ed. Chicago: Year Book Medical Publishers; 1986. p. 265-76.

19 Duval M. Le placenta des rongerous. *J Anat Physiol*. 1891;27:612.

20 Teilum G. Endodermal sinus tumors of the ovary and testis: Comparative morphogenesis of the so-called mesonephroma ovarii (Schiller) and extraembryonic (yolk sac-allantoic) structures of the rat's placenta. *Cancer*. 1959;12:1092-105.

21 Steinmann W. Ein Fall von Sakralteratom. Dissertation. Marburg; 1905.

22 Tapper D, Lack EE. Teratomas in infancy and childhood. A 54-year experience at the Children's Hospital Medical Center. *Ann Surg*. 1983;198(3):398-410.

23 Gonzales-Crussi F. Extragonadal Teratomas. Atlas of Tumour Pathology, sec series, fascicle 18. Washington D.C.: Armed Forces Institute for Pathology; 1982.

24 Gurney JG, Bondy ML. Epidemiology of Childhood and Adolescent Cancer. In: Behrman RE, editor. Nelson Textbook of Pediatrics, 17th ed. Madison: WB Saunders; 2003. p. 1679-81.

25 Beckwith JB, Perrin EV. In situ neuroblastomas: A contribution to natural history of neural crest tumours. *Am J Pathol*. 1963;43:1089-94.

26 Haas D, Ablin AR, Miller C. Complete pathologic maturation and regression of stage IVS neuroblastoma without treatment. *Cancer*. 1988;62:818-23.

27 Coffin CM, Dehner LP. Soft tissue tumours in first year of life: a report of 190 cases. *Pediatr Pathol*. 1990;10:509-15.

28 Harmer MH, editor. TNM Classification of Paediatric Tumours. Geneva: UICC International Union Against Cancer; 1982.

29 Hermanek P, Sobin I, editors. TNM Classification of Malignant Tumours. Berlin: Springer; 1987.

30 Jaffe N. Cancer Chemotherapy. In: Welch KJ, et al, edotors. Pediatric Surgery, Vol 1. 4th ed. Chicago: Year Book Medical Publishers; 1986. p. 241-8.

31 D'Angio GJ. Radiation Therapy for Solid Tumours. In: Welch KJ, editor. Pediatric Surgery, Vol 1. 4th ed. Chicago: Year Book Medical Publishers; 1986. p. 249-55.

32 Boice JD Jr, Green MH. Leukemia and pre-leukemia after adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU). *N Engl J Med*. 1983;309:1079-84.

33 Schag C, Heinrich R, Ganz P. Karnofsky performance status revised: reliability, validity, and guidelines. *J Clin Oncol*. 1984;2:187-93.

34 Lansky L, List M, Lansky S, Cohen M, Sinks L. Toward the development of a play performance scale for children. *Cancer*. 1985;60;1837-40.

35 Lansky S, List M, Lansky L, Ritter Sterr C, Miller D. The measurement of performance in childhood cancer patients. *Cancer*. 1987;60:1651-6.

36 Bleyer A. Principles of Treatment. In: Behrman RE, editor. Nelson Textbook of Pediatrics, 17th ed. Madison: WB Saunders; 2003. p.1688-93.

37 Worth LL. Molecular and Cellular Biology of Cancer. In: Behrman RE, editor. Nelson Textbook of Pediatrics, 17th ed. Madison: WB Saunders; 2003. p.1682-5.

38 Malkin D, Li FP, Strong LC. Germ line p53 mutations in a familial syndrome of breast cancer, sarcoma and other neoplasms. *Science*. 1990;250:1233-9.

39 Nowel PC, Hungerdorf DA. A minute human chromosome in human granulocitic leucemia. *Science*. 1960;132:1947.

40 Francke U. A gene for Wilms' tumor? *Nature*. 1990;343:692-6.