Diagnosis errors in renal tumors in children

Gudumac E.[1,2,3], **Bernic J.**[1, 3], **Petrovici V.**[4], **Curajos B.**[1, 3], **Roller V.**[2, 3]

Nicolae Testemitanu SUMPh, Department of Surgery, Orthopedics and Pediatric Anesthesia[1],
Laboratory of Surgical Infections in Children[2],
PHI Institute of Mother and Child, Academician Natalia Gheorghiu National Scientific and Practical Center for Pediatric Surgery[3,]
Department of Morphopathology[4]

Abstract

Erori de diagnostic în tumorile renale la copii

Diagnosticul, tratamentul şi profilaxia patologiei canceroase, în special la copii rămâne o problemă de sănătate publică majoră atât la nivel global, regional, cât şi naţional, inclusiv în Republica Moldova. Tumorile retroperitoniale, în special renale la copii frecvent atestă un patern malign rămân în continuare discuție privind diagnosticarea clinico-paraclinică în timpi oportuni. Revizuirea activității diagnostice a unui eșantion de 62 pacienți întro perioadă de 10 ani a stabilit frecvența și structura tumorilor renale la copii, în 15% din cazuri sa atestat persistarea unui diagnostic întârziat, cauzat de diverse erori atestate la diverse nivele ale asistenței medicale, determinând spitalizarea înârziată în subdiviziunile medicale specializate. În rezultatul studiului și a cauzelor atestate în prevenirea unor erori, în baza protocaolelor NWI'S și SIOP sa elaborat o nouă conduită prevăzând și particularitățile diagnosticului histopatologic după noua clasivicare privind paternul histopatologic al tumorii care va reduce posibilele deficultăți diagnostice spre un management diagnostic și medico-chirurgical oportun.
Cuvinte cheie: tumorile renale, diagnostic, tratament, profilaxie, copii

Abstract

The diagnosis, treatment and prophylaxis of cancer pathology, especially in children, remains a major public health issue on the global, regional and national level, including in the Republic of Moldova. Retroperitoneal tumors, especially those renal in children, frequently attest to a malignant pattern and there remains a discussion of clinical-paraclinical diagnosis over time. The review of the diagnostic activity of a sample of 62 patients over a period of 10 years determined the frequency and structure of kidney tumors in children, in 15% of cases the persistence of a delayed diagnosis, caused by various errors at different levels of health care, delayed in specialized medical subdivisions, was attested. As a result of the study and of the proven cases in the prevention of errors, based on the NWI'S and SIOP protocols, a new behavior was developed, including the histopathological diagnosis features after the new histopathological pathology classification of the tumor, which will reduce the possible diagnostic deficits towards a timely diagnostic and medical-surgical management.
Keywolrds: renal tumors, diagnosis, treatment, prophylaxis, children

Correspondence to: e-mail: victorroller.vr@gmail.com; mob.: +37369354951

Introduction

Tumors of the renal-ureteral and neurogenic system in children are the most frequent tumors of the retroperitoneal space, characterized by various expansions to or in the abdominal cavity, mimicking gastro-duodenal, mesenteric, colon. Both retroperitoneal or intraabdominal locations frequently have a common general symptom. At the same time, retroperitoneal tumors in children, especially reno-ureteral, are much more common compared to mesenteric, colonial or gastro-duodenal. Tumors with renal localization in childhood ontogenesis account for about 5-11% of the total attested tumors at this age [10]. According to the literature, Wilms tumor (nefroblastoma) is the most common kidney tumor in childhood in over 90% of cases of kidney tumor [5]. The annual incidence is 8.1 to one million children, resulting in 600-700 new cases each year in the North America. Symptomatic manifestations of the tumor more frequently occur at the age of 1-4 years, the mean age at diagnosis of children with Wilms tumor of 3 years, being relatively unusual in the first 6 months and in children aged 6-10 years [3, 4]. A large number of children diagnosed with kidney tumor consult a physician with various symptoms, which depending on location, age and level of healthcare are initially treated as manifestations of other abdominal processes, which induces late diagnosis of renal tumor. According to statistical data, about 60,000 people with kidney tumor, including malignant, are diagnosed lately, often in late stages, and are confused with other conditions, including kidney malformations [6, 11]. Causes that can lead to diagnostic errors are multiple, including limited time spent on a consultation, incomplete examination, incorrect interpretation of imaging data, vasography, etc. The medical practice demonstrates that there is currently no evidence of clinical and paraclinical moments in making the delayed, erroneous or inappropriate diagnosis of tumor pathology in children, which justified the retrospective analysis of the problem.

The aim of the study was to evaluate the diagnostic activity, the morphology and morphopathology aspects of the renal tumors, to determine and avoid delayed diagnostic or diagnosis errors, to optimize the medical and surgical diagnosis of kidney tumors in children.

Material and methods

The data provided from the observation sheets, the children's development card, the previous exit tickets, the anamnesis, the personal evaluation, the diagnosis and the treatment, all processed statistically, served as materials for the study. The study was conducted within the Urology Department of PHI Academician Natalia Gheorghiu National Scientific and Practical Center for Pediatric Surgery on a sample of 62 children aged between 2 weeks and 18 years who were diagnosed with renal tumors during 2007-2017. As a significant objective, this study included the elucidation of some risk factors in the development of renal tumors from the study group, the development of an appropriate correlation of diagnostic methods, treatment in the assessment of prognosis in kidney tumors in the child.

Results and discussions

As a result of the examination, the prevalence of male renal tumors predominantly constituted 54.8% (34 boys) compared to 45.3% (28 girls). 32.3% (20) of cases predominated between the age of 5 and 7 months, and 45.2% of children aged 3 to 5 years (28 cases). A frequency with statistical significance was renal tumor diagnosed in 22.6% (14 cases) in the infant's age from 2 weeks to 4 months. According to the data indicated in 87.1% (54) of medical records, 79.9% (41) of the children were born at term of 39-40 weeks, 18.5% (10) at term of 37-38 weeks and 5.6% (3) children were born at the 35-37 week limit.

Depending on the location of the tumor with a frequency of 62.3% (38 cases), the renal tumor affected the left kidney compared to the right kidney - 35.5% (22) of the cases. A case in our observations and medical diagnosis was the detection in 2 (3.3%) of cases of bilateral tumor localization.

In 35.5% (22) of primary diagnosed children, renal tumors were primarily surgically resolved, and in 64.5% (40) of cases due to delayed and difficult diagnosis, some complications were caused by the tumor and other circumstances. The children initially had a chemotherapy treatment, which led to a prognosis reserved for this category of children, as well as some difficulties in the correct treatment, including establishing the histopathological specific pattern.

Depending on the duration of the premorbid and morbid status in 32.3% (20) of cases, the presence of the renal tumor was suspected and / or diagnosed by the pediatrician or the family doctor to whom the parents addressed for various reasons. In 30.6% (19) of cases, the development or presence of a bulky expansion process and abdominal asymmetry were primarily reported by parents and later diagnosed by the doctor as renal tumor at different periods from the onset of manifestations observed by the parents. Another partiality of digagnostics in 35.5% (22) cases was the occasional diagnosis of renal tumors in the routine ultrasound of internal organs, and retrospectively referred to by parents as a general unstable symptomatology. In one case, 1.6% of the kidney disease was suggestively suspected as a malformation still at the USG in the perinatal period, and subsequently in the first year of life being confirmed as a renal tumor.

According to anamnesis and in-patient assessment, clinical symptomatology in the study group had a varied

and non-specific onset. In 48.4% (30) of cases, children showed a general symptom characterized by the persistence of a abdominal algic syndrome, apathy, subfebrility, fatigue, observed in the last 1-4 months. In 30.6% (19) of cases in parallel there were more obvious digestive disorders - dyspepsia and vomiting during 1-3 months. At a rate of 8.1% (5 cases), renal tumor evolution evolved hidden under the acute abdomen and 3.2% (2) cases of abdominal trauma in connection with what was urgently hospitalized in the Mother and Child Institute. In 6.5% (4 cases), the evolution indicated the presence of a renal tumor, which was occasionally detected in ultrasound examinations (USG) in the absence of premorbid status.

According to the morphological imaging data (fig. 1, 2) and morphopathological retrospectives in 50.0% of the children, the renal dimensional tumor varied within the limits of 4x5cm, with 37.1% within the limits of 8x7cm. 12.9% of children were confirmed with major and impressive tumors, of which 8.1% were 14x10cm and in 4.8% of cases in the limits of 11.5x7.5cm.

Another feature attestable at the time of tumor diagnosis was the presence of a significant correlation between the tumor dimensions and the parenchyma of the kidney, which recorded 72.6% (45) of cases a tumor cortex between 35-60% of the renal area and in a frequency of 27.4% (17) of children with a larger area of 60-70% compared to renal parenchyma, of which in 3 cases the tumor occupied about 90% of the renal mass with a weight of 370.0g and 420.0g

.

We note that in 2 children (3.2%) aged 1 to 3 months the presence of the renal tumor was diagnosed with delay, the diagnosis being difficult only for the USG method, therefore, computerized tomography (CT) with vaseography was used. Surgical interventions in all cases were performed in accordance with the morbid tumor status of children, the anatomic features of the deformed tumor kidney according to the procedures provided by the national and international protocols (fig. 3, 4). According to the morphopathological pattern of kidney tumors, there were determined nephroblastic tumors - 48.4%, 19.6% - mesenchymal tumors, 18.3% - mesenchymal epithelial tumor, 13.8% - mixed tumors. Focal hemorrhagic necrosis, necrotic ischemic processes, and some inflammatory associations of the tumor and renal parenchyma were confirmed in 59.2% of tumor cases (fig. 3). In 23.6% of cases, very rare variations were observed, such as mesenchymal blast-epithelial mixed nephroblastoma, stromal epithelial nephritis, cystic multilocular nephroma, blastic neproroblastoma associated with fibroadenoma (fig. 4-6). In our case, on the diagnosis of kidney tumors in children, there was also the diagnosis of kidney tumor in 2 children of the same family (both girls) - the first underwent a surgery of a primary diagnosed kidney tumor, and in the second girl the tumor was determined after examination at the doctor's indication far more late, being diagnosed the presence of bilateral renal tumor, the child was hospitalized for evidence and solving at the Institute of Oncology.

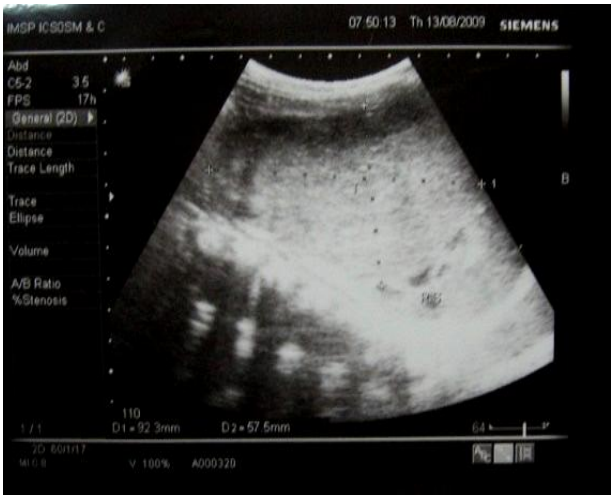

Fig. 1. Renal ultrasonography. Patient S. Renal tumor on the right without signs of vessel thrombosis

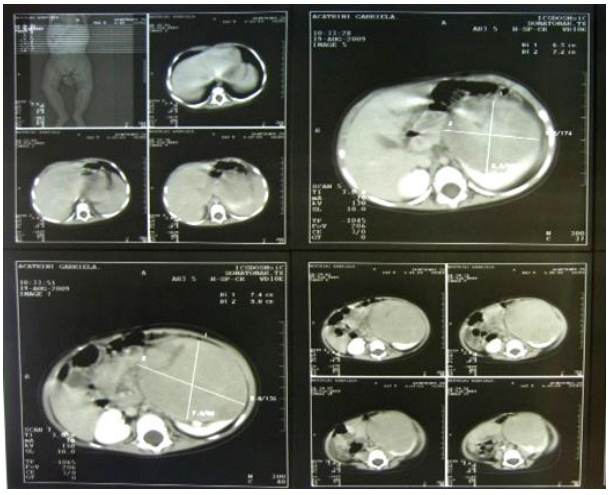

Fig. 2. CT. Patient A. CT aspect of right kidney tumor

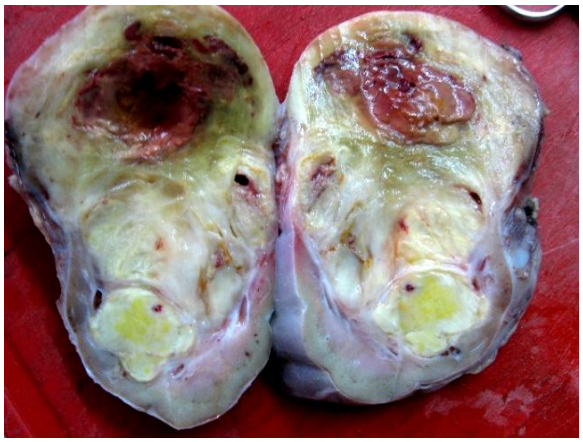

Fig. 3. Patient N. 1 year old (no. 43/278). Mesoblastic nephrom of the left kidney with thrombosis and haemorrhage

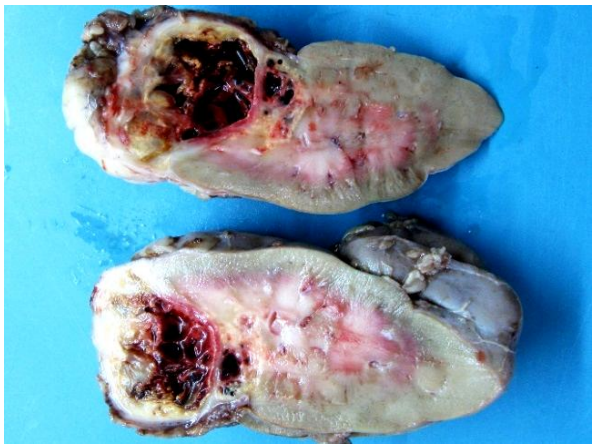

Fig. 4. Patient S., 5 years old (no.4087 / 19250). Blast-epithelial mixed nephroblastoma with mesenchymal component. After 2 chemotherapy treatments

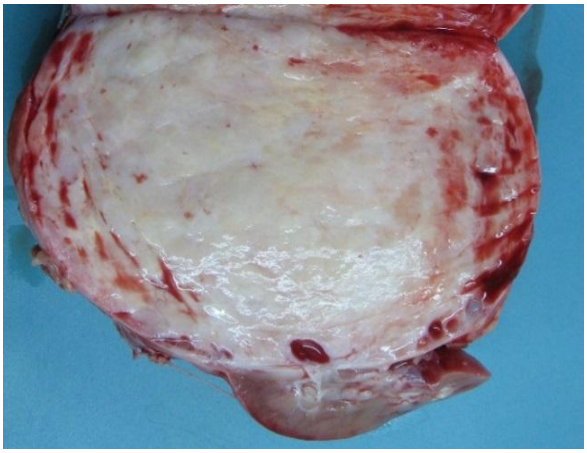

Fig. 5. Patient C, 2 years old (no.1294/6486). Mezenchimal-epithelial nephrom of the left cystic focal kidney.

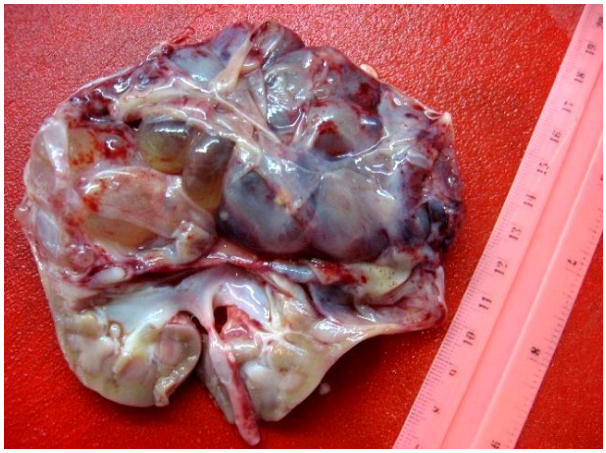

Fig. 6. Patient M., 3 years old (No. 846/5467), cystic formation. The tumor is polycystic and is separated from renal parenchyma by a fibrous capsule

However, we note that 6-7 decades ago, kidney tumor mortality varied between 70-75%, currently due to protocols developed by the Wilms National Research Group (NWI'S) used in the United States of America, Canada and those developed by the International Society for Pediatric Oncology (SIOP) used in European countries, mortality has significantly decreased, in 80% of cases, patients are treated with initial chemotherapy. Survival is similar in some of the protocols, currently being 900 / o.m [2, 7, 8]. The NWI'S protocol is directed to performing nephrectomy and establishing the morphopathologic diagnosis in optimal time, the one proposed by SIOP provides for initial treatment with adjuvant chemotherapy [8].

Morphopathological diagnosis is based on the absence or presence of blastem-epithelial elements or anaplasia, depending on which tumors are divided into tumors with favorable and unfavorable histology [9]. According to some studies, cellular anaplasia occurs with a frequency of 11% of cases of Wilms tumor. According to the SIOP protocols, patients with Wilms tumors with a favorable histological pattern, ie characterized by a low epithelial-blastomatoid component, or the predominance of epithelial-stromal cells only after preoperative chemotherapy have a better prognosis than those with large amounts of cellular blast in tumors [1]. In the evaluation of 15% (9) of the cases, some discrepancies, regarding the operational

management and the diagnostic opportunity, including in the cases of abdominal trauma, were found (2 cases fig. 3-5).

Clinical case reporting: The female patient, S.A, aged 1 year and 5 months, (fig. 7), was hospitalized urgently after 10 days of having occasionally sustained a lumbar traumatism injury on the right of the table horn (according to the parents). The child was evaluated by the family doctor. Ultrasound of the urinary system was performed - without any obvious pathological changes, being left in out-patient conditions. Upon admission to the Mother and Child Institute, the general condition is confirmed, it is severe, periodically subfebrile, pale skin and mucous membranes. Heavy breathing in the lungs. The cord - no stealthy noises. The asymmetric abdomen, enlarged in dimensions in the hippocampus and the right flank, the pronounced vascular drawing with venous stasis, the abdominal wall in the precordial area (fig.7). Palpation of the abdomen detects a tough, irregular, sensitive tumor, located in the abdomen on the right. Electrocardiogram at admission - no changes, sinus rhythm.

Biological status examinations: Anemia, increased VHS (Hb.-98 g / l; Er.-2.3x1012 / l; L. 7.4x10 9 / l, non-segm. -7.0, segm. - 8, VSH - 15mm / h, total protein - 64 g / l, serum urate - 4.3, serum creatinine - 0.057 mmol / l, bilirubin - 9.4 mcmol, transaminase - l, Na - 141 mmol / l). The imaging examinations revealed: Doppler ultrasound - the formation as intense vascularized arterial and venous without signs of thrombosis in the renal vein; CT - kidney tumor of the right kidney of major size 14x10 cm. General urine test: color - yellow, transparent, reaction - acid, protein - negative, flat epithelium - unique in the field of view, leukocytes - 2-4 in the field of view. Taking into account the generally appreciated serious condition, the major dimensions of the tumor, the previous trauma, the consultation of the pediatrician, chemotherapy was done in the Department of Pediatric Oncology of the Institute of Oncology. After three chemotherapy treatments (vincristine - 0.75 mg on the 1st, 8th, 5th days and adriamycin- 20 mg on the 15th day), surgical treatment followed by transabdominal approach on the right (fig. 8-10). On the day of surgery, the asymmetric and enlarged in size abdomen persists in the hippocampus and the right flank, palpating the same tumor-specific features (fig.7).

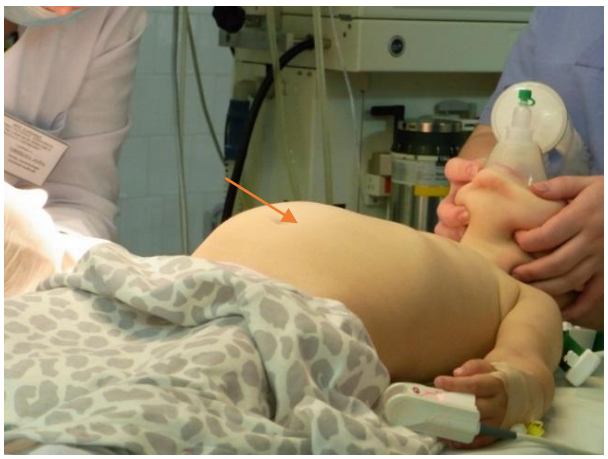

Fig. 7. Patient S. On the day of surgery. Abdominal expansion on the right

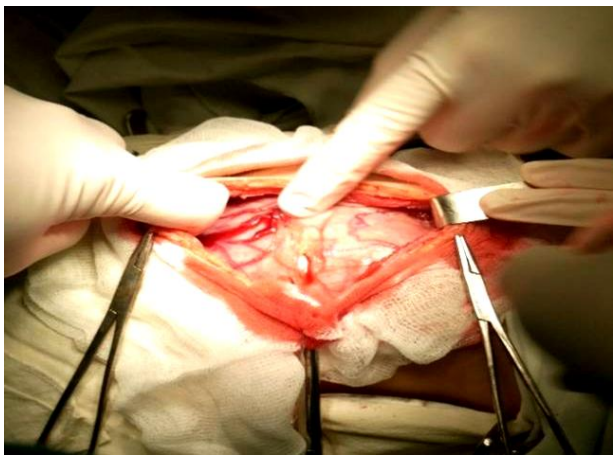

Fig. 8. Intraoperative aspect of the renal tumor in the incision

The post-operative period evolved without any local or general complications, 8 days after the surgery, the patient was transferred to the Oncology Department of the PHI Oncology Institute to continue the chemotherapy treatment and to rigorously check the renal function along the way.

Therefore, the case at first glance, presents a difficult and delayed diagnostic management in a child with Wilms tumor (mesoblastic nephroblastoma), retrospectively made. These cases in medical diagnosis are frequently treated as diagnostic errors. Currently, according to the specialty literature, the majority opinion considers that the wrong diagnosis should be replaced by the medical error because the diagnosis is based on the signs and symptoms identified when the patient is present at the doctor, as well as by the communicable aspect of the parents. On this subject Mr. Prof. Vasile Astarastoaie, the president of the Romanian College of Physicians, states that "The systemic approach to the disease is totally lacking" [6].

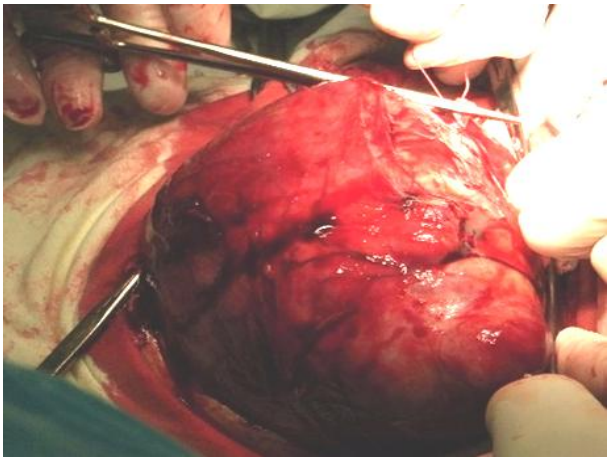

Fig. 9. Ablație a vaselor, legătura picioruşului vascular reno-tumoral

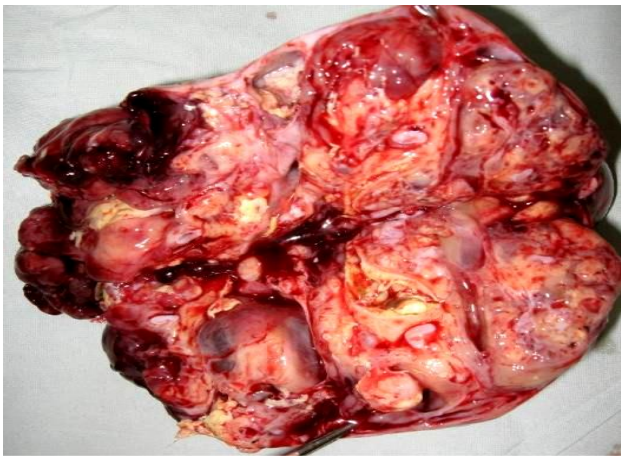

Fig. 10. Piesa anatomo-chirurgicală a tumorii în secțiune

However, we mention that early diagnosis of a kidney tumor, especially Wilms' Tumor, including its variations, is very important because it will have a better prognosis and a more favorable post-procedural or post-interventional evolution. At the same time, despite the fact that many patients show statistically favorable post- procedural or post-interventional evolution, but the medium and long-term prognosis seems to be unfavorable in most cases.

The Wilms tumor, defined by Beekwith (1975) as a renal tumor, is composed of metanephrogen blast and its stromal and epithelial derivatives, at different stages of differentiation, which give it a histopathological pattern in different variations, attested in our practice as well. It is known that environmental factors do not play an important role in tumor development or histopathological changes. Currently, it is indicated in a genetic predisposition with a determined role in tumor development.

Research on histological classification, staging schemes, early diagnosis, initial stages (TNoMo, T2 NoMo) have a fatal histology and an unfavorable prognosis. The favorable progression may be in the case of small areas of neoplasms, cellular aplasia and small focal areas of penetration of the capsule. Thus, the prognosis is unaffected first, depending on the size of the tumor and its weight. The most unfavorable factors are: the age of the child in the tumor, the advanced stage of the tumor and the unfavorable histopathological pattern.

Therefore, the results we have obtained in our study and our clinic experience together with literature data, taking into account the international protocols recommended by NWI'S of the US and the European SIOPs, make us recommend a more cautious assessment of children who have abdominal pain, haematuria, constipation, urinary tract infection, diarrhea, presence of trauma in anamnesis expansion or palpation of a formation in the abdomen, etc. Therefore, the medical-surgical tactic in cases with the aforementioned symptomatology is suggestive of the tumor or in those occasionally detected or suspected will include the following:

- Anamnesis (perinatal development, presence of tumors or anomalies in family members, relatives, evolution of symptomatic morbid status, etc.);
- Anthropometric, weight, functional cardio-respiratory examinations etc .;
- Laboratory blood counts, urine summary exam, coagulogram, creatinine, etc .;
- USG imaging investigations of abdominal cavity and retro-peritoneal space;
- Computerized (CT) CT scan with contrast, chest CT in difficult or complicated cases, including MRT (on indication), Kidney Renoscintigraphy;
- Puncture-biopsy of the tumor formation under ultrasound guidance, with a 2-3 point score to establish the tumor parenchymal pathway (favorable, standard, unfavorable according to NWI'S and SIOP), except in cases of cystic tumor.

Conducting in such order and urgently will allow the assessment of the general condition of the patient, the location of the tumor and the degree of spread, the morphopathological confirmation of the tumor pattern, on which the medical-surgical tactic and prognosis of the disease will depend.

The medical-surgical treatment tactic, after making the diagnosis, will be performed according to the complex program: surgery, chemotherapy, radiotherapy.

Conclusions. The study concluded, that during the last 10 years in the Republic of Moldova, as well as in many countries of the world, there is an increase in the number of kidney tumors, especially of nefroblastoma in different morphopathological variations at different ages. The widespread use of

imaging methods has led to an increase in the diagnosis rate of renal tumors in incipient stages and in children aged 0-1 year, yet an impressive number of tumors are diagnosed late and are a pressing problem of medical diagnosis. As a result of the study, according to NWI'S and SIOP, a follow-up of the work of pediatricians, family doctors, and special care physicians, was carefully quantified for the careful consideration of children, in order to determine, as early as possible, the features of retroperitonial kidney tumors in children, in order to prevent diagnostic errors and possible complications.

REFERENCES

1. Breslow N.E., Palmer N.F., Hill L.R., et al. W!lms' tumor: prognostic factJm for patients without metastases at diagnosis, results of the National Wilms' Tumor Study. *Cancer*. 1978; 41:1577-89.
2. Gadd S., Huff V., Huang C-C., et al. Clinically relevant subselll identified by gene expression patterns support a revised ontogenic model of Wilms tumor: a Children's Oncology Group study. *Neoplasia.* 2012; 14: 742-56.
3. Hrabovsky E.E., Othersen H.B. Jr., deLorimier A., et al. Wilms' tumor in the neonate: a report from the National Wilms' Tumor Study. *J. Pediatr. Surg.* 1986; 21:385-7.
4. Nocol P.F., Rollins M.D., Muratore C.S. Fundamentals of Pediatrics Surgery, Springer International Publishing. 2017; p. 777-86.
5. Pastore G., Znaor A.. Spreafico F., et al. Malignant renal tumours incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System Project. *Eur. J. Cancer*. 2006; 42:2103-14.
6. Programul Național de control al canceruluipentruanii 2016-2015. HotărîreaGuvernuluinr. 1291 din 2 decembrie, 2016.
7. Shannon B.A., Cohen R.J., Segal A., et al. Clear cell renal cell carcinomawith smooth muscle stroma. *Hum. Pathol.* 2009; 40;425-9.
8. Sonn G., Shortliffe L.M.D. Management of Wilms tumor: current standard of care. *Nat. Clin. Pract. Urol.* 2008; 5 :551-60.
9. Verschuur A.C., Vujanici G.M., van Tinteren H., et al. Stromal and epithelial predominant Wilms tumours have an excellent outcome: theSlOP 93 01 experience. *Pediatr. Blood Cancer*. 2010; 55:233-8.
10. Ивановская Т.Е., Леонова Л.В Патологическая анатомия болезни плода и ребенка. *М.: Медицина*. 1987; 256с.
11. Пытель Ю.А, Золотарев И.И Ошибки и осложнения в рентгенослогическом исследовании почек и мочевых путей. *М.: Медицина.* 1987; 256с.