Case Report

Kidney atrophy after retroperitoneal neuroblastoma resection in children. Clinical case presentation and literature review

Babuci S.,[1, 2] **Jalba A.,**[2] **Roller V.,**[2] **Negru I.**[1]

PHI Mother and Child Institute[1]
"Natalia Gheorghiu" National Scientific and Practical Center of Pediatric Surgery
"Nicolae Testemitanu" State University of Medicine and Pharmacy[2]
"Surgical Infections in Children" Laboratory

Abstract

Atrofia renală după rezecția neuroblastomului retroperitoneal la copil.
Prezentare de caz clinic și revista literaturii

Neuroblastomul (NB) reprezintă cea mai frecventă tumoră solidă malignă extracraniană la copii. În cazurile unui tratament chirurgical radical asociat cu chimioterapie și/sau radioterapie există riscul dezvoltării unor complicații tardive, inclusiv cele renale ipsilaterale. În acest context autorii prezintă următorul caz clinic.
Pacienta E., în vârstă de 3 ani, a fost internată pentru o formațiune tumorală abdominală depistată la ecografie abdominală și confirmată la CT spiralată cu contrast a abdomenului, diagnosticul imagistic fiind sugestiv pentru o formațiune tumorală retroperitoneală fără semne clare de agresiune, posibil ganglioneurom; pieloectazie stângă moderată.
Copilul a fost supus intervenției chirurgicalet. Sub anestezie endotraheală generală s-a efectuat o laparotomie transrectală stângă, cu îndepărtarea completă a tumorii fără leziunea capsulei tumorii și vasele renale cu păstrarea rinichiul stâng. Ulterior, a fost exciziată a doua formațiune. Tratamentul chimioterapeutic a fost tolerat relativ satisfăcător, cu dezvoltarea agranulocitozei moderate. După a treia serie de chimioterapie, examenul ecografic a constatat micșorarea în volum a rinichiului stâng. La RMN, efectuată după a patra serie de chimioterapie, a pus în evidență lipsa recidivei tumorii, aspectul hipoplazic al rinichiul stâng, care avea dimensiuni de 36 x 15 mm, cu pierderea diferențierii stratului cortico-medular. Secvențele postcontrast au atestat contrastarea slabă a parenchimului renal stâng.
Concluzie. Intervenția chirurgicală radicală urmată de chimioterapie a permis de a asigura un control local benefic în neuroblastomul retroperitoneal slab diferențiat cu metastaze în ganglionii limfatici regionali la un copil cu vârsta peste 18 luni. În cazurile de rezecție radicală a neuroblastomului retroperitoneal de dimensiuni majore există riscul dezvoltării unor complicații postoperatorii renale, inclusiv a atrofiei renale. Dislocarea rinichiului cu comprimarea tumorală a hilului renal, inclusiv a vaselor renale, poate fi considerat un factor de risc predictor de dezvoltare a atrofiei renale postoperatorii ipsilaterale la copiii cu neuroblastom retroperitoneal de dimensiuni majore.

Cuvinte cheie: neuroblastom retroperitoneal, chirurgie, complicații, atrofie renală, copii

Abstract

Neuroblastoma (NB) is the most common extracranial malignant solid tumor in children. In cases of radical surgical treatment associated with chemotherapy and / or radiotherapy there is a risk of developing late complications, including ipsilateral renal complications. In this context, the authors present the following clinical case.

Patient E., aged 3 years, was hospitalized for an abdominal tumor formation detected on abdominal ultrasound and confirmed on spiral CT with contrast of the abdomen, the imaging diagnosis being suggestive for a retroperitoneal tumor formation without clear signs of aggression, possibly ganglioneuroma; moderate left pyeloectasia. The child underwent surgery. Under general endotracheal anesthesia, a left transrectal laparotomy was performed, the tumor was completely removed without injuring the tumor capsule and renal vessels while keeping the left kidney in place. Subsequently, the second mass was excised. Chemotherapeutic treatment was relatively well tolerated with the development of moderate agranulocytosis. After the third cycle of chemotherapy, the ultrasound examination revealed a reduction of the left kidney. On MRI, performed after four courses of chemotherapy, there were not signs of recurrence, the left kidney was hypoplastic, (the size 36 x 15 mm), with loss of cortico-medullary layer differentiation. Postcontrast sequences showed poor contrasting of the left renal parenchyma.

Conclusion. Radical surgery followed by chemotherapy ensured a beneficial local control in poorly differentiated retroperitoneal neuroblastoma with metastases in the regional lymph nodes in a child over 18 months of age. In cases of radical resection of major retroperitoneal neuroblastoma there is a risk of developing postoperative renal complications, including renal atrophy. Dislocation of the kidney with tumor compression of the renal hilum, including the renal vessels, may be considered a predictive risk factor for the development of ipsilateral postoperative renal atrophy in children with major retroperitoneal neuroblastoma.

Keywords: **retroperitoneal** neuroblastoma, surgery, complication, kidney atrophy, children

Correspondence to: e-mail: babucistanislav1@gmail.com

Neuroblastoma (NB) is the most common extracranial malignant solid tumor in children [30, 42], this embryonic neoplasm originating from the primitive neuroectodermal cells of the neural crest from which the sympathetic nervous system and adrenal medulla are differentiated [16, 35]. NB can be located in the cervical, intrathoracic, intra-abdominal, retroperitoneal or pelvic regions [5].

This heterogeneous tumor represents about 8-10% of all cases of malignancies and 15% of the total number of deaths in children with various forms of cancer, with an estimated incidence of 1 case per 10,000 live births [4, 17, 24]. The average age of onset of the disease is 18 months [53]. In the morbidity structure of children up to 1 year of age, NB constitutes about 26% of malignant tumors [52]. About 50% of NB cases are diagnosed in children up to the age of 2 years [53], over 90% of cases being found in the first 5 years of life, with different clinical behaviors such as: progressive evolution and metastasis, spontaneous regression or maturation in ganglioneuroma, this phenomenon being first described in 1927 by Cushing H. and Wolbach S.B. [22, 31, 53]. Over 50% of children with NB have metastatic disease [49]. After the age of 15 years and in adults it is described as a rare entity [27, 46]. Usually, neuroblastoma is a sporadic tumor, but 1-2% of patients have a family history of the disease [1]. The prognosis of this neoplasm varies depending on the stage and the biological and morphopathological characteristics of the tumor [26]. Low and intermediate risk forms of NB have been well managed being surgically resolved, long-term survival rates being about 90%, while in high-risk forms the total survival rate of five years after multimodal surgical and non-surgical treatment is about 40% -50% [39]. At the same time, in cases of radical surgical treatment associated with chemotherapy and / or radiotherapy there is a risk of developing of late complications, including ipsilateral renal complications, such as renal hypoplasia or even insidious ipsilateral renal atrophy with the development of renal failure [14, 20, 21]. In this context we present the following clinical case.

Patient E., 3 years old, was consulted at the end of 2019 for intermittent abdominal pain at the PHI Mother and Child Institute consultative center, where an abdominal ultrasound showed an abdominal tumor. The contrasting spiral CT of the abdomen revealed the presence of a massive solid tumor, located retroperitoneally on the left (Th11-L3), was polylobulated, well contoured with the following size - 7.2 cm (vertical) x 6.2 cm (transverse) x 4, 5 cm (anterior-posterior). Texturally heterogeneous, the tumor contained multiple hypodense areas (possibly necrolithic), intrastromal calcinations, without invasion in the spinal canal, the native density being + 40UH with post-contrast amplification in the late phase + 62UH. The afferent and efferent vessels were undetectable. The mass effect was characterized by posterior dislocation of the

left kidney with moderate compression of the renal hilum, moderate dilation of the left renal pelvis. The left renal artery was posteriorly displaced, renal vein - caudally dislocated, and an anterior displaced supernumerary artery participated in vascularization of the lower pole of the kidney. Also the moderate upper displacement of the pancreas, spleen artery and vein was found out, without clear signs of invasion, and CT image was suggestive of a left sided retroperitoneal tumor without signs of aggression, possibly ganglioneuroma; moderate left pyeloectasia (fig. 1).

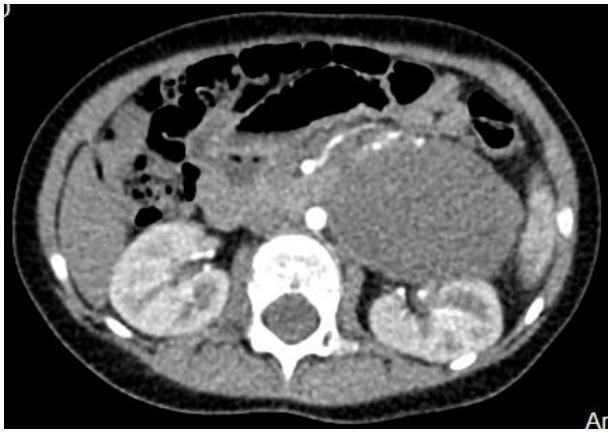


Fig. 1. Patient E., 3 years. Contrasted spiral CT of the abdomen (explanations in text)

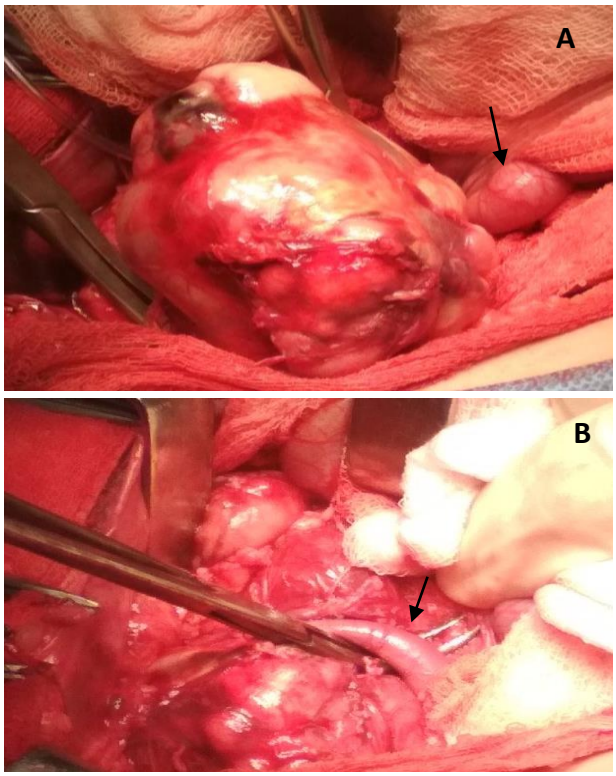


Fig. 2. Intraoperative appearance of retroperitoneal tumor after mobilization (A) with a smaller adjacent mass (arrow); B - blood vessel crossing the lower pole of the tumor (arrow)

With the diagnosis described above, the child was hospitalized. It was found out that the child complained of abdominal pain for half a year. The child was afebrile without vomiting and fever. Other diseases were not diagnosed. On inspection, the abdomen was normal, palpation revealed a hard consistency tumor, which was painless, adherent to the deep planes and located in the left flank. The peripheral lymph nodes were of normal size. Chest radiography didn't show pathological changes, except the fact that in the left axillary fossa, in the lymph nodes were found impregnations of calcium salts which was treated as BCG sequelae. Hematological and urine lab tests were without any significant pathological changes. The child underwent surgery. Under general endotracheal anesthesia, a left transrectal laparotomy was performed. After opening the peritoneal cavity and the left retroperitoneal space, the surgical exploration found an oval encapsulated tumor (fig. 2A), circumferentially vascularized from multiple sources, which compressed the left kidney and renal vessels without involving the adrenal gland. The lower edge of the tumor was crossed by a medium-sized blood vessel, which was participating in the vascularization of the lower pole of the kidney (fig. 2 B). Below the tumor, another mass was observed, measuring 1.2 x 1.0 cm. After careful mobilization of adjacent tissues by combining the blunt dissection and the electrocoagulator, the tumor was completely removed without injuring the tumor capsule and renal vessels, the left kidney was left in place. Subsequently, the second mass was excised. After hemostasis, other retroperitoneal or intra-abdominal masses or enlarged lymph nodes were not identified. The integrity of the peritoneum was restored with the application of a tubular drainage in the abdominal cavity and the restoration of the anatomical planes.

Histopathological examination established the diagnosis of poorly differentiated neuroblastoma (poor in Schwanian stroma), later confirmed by immunohistochemical investigations. Postoperative recovery was without severe complications, except for a pronounced abdominal distension developed on the 2nd postoperative day which was resolved conservatively.

The patient was discharged on the tenth day. Subsequently, the patient underwent chemotherapeutic treatment and regular supervision in the profile institution. Chemotherapeutic treatment was relatively well tolerated with the development of moderate agranulocytosis. After the third cycle of chemotherapy, the ultrasound examination found a reduction of the left kidney size, which was about 48x18 mm. On MRI, performed after the fourth course of chemotherapy, there were not signs of recurrence, the left kidney was hypoplastic, of 36 x 15 mm, with the loss of cortico-medullary layer differentiation. Postcontrast sequences showed poor contrasting of the left renal parenchyma (fig. 3).

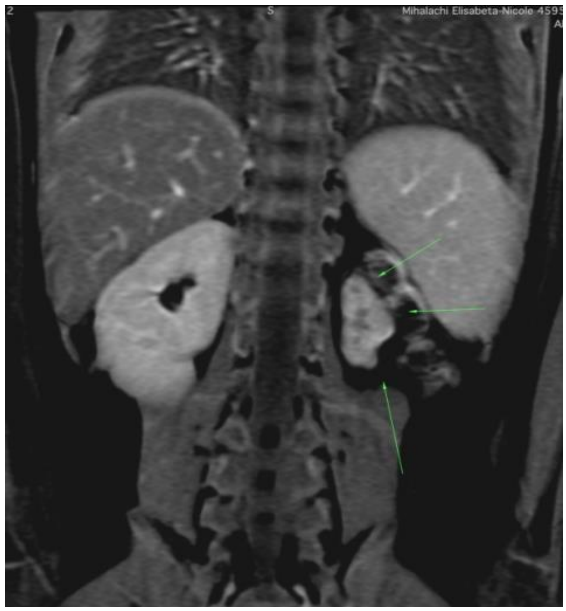
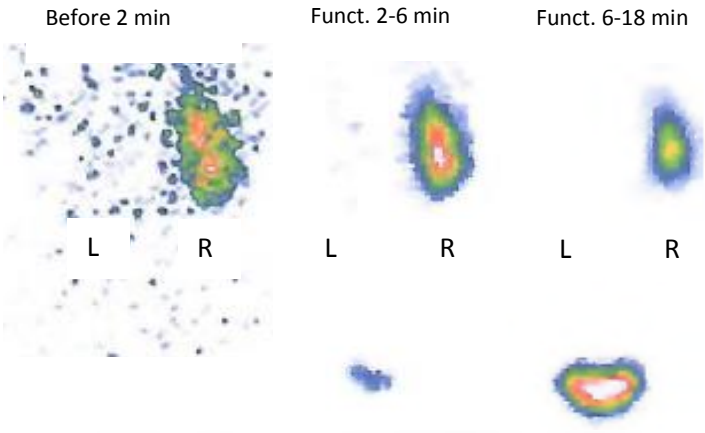


Fig. 3. Patient E., MRI performed at 6 months postoperatively. Left kidney atrophy found (explanations in text)



	Left	Right
T0 (sec):		0
Tmax:		2'30"
Thalf:		14'05"
Wash-out Thalf:		10'10"
Residual Activity:		29.9 %
Norm.Res. Activity:		29.9 %

Fig. 4. Patient E. Dynamic renal scintigraphy performed 1 year after surgery (explanations in the text).

Angiographic reconstruction did not visualize the left renal artery. One year after surgery, CT found no signs of tumor recurrence or metastasis. On dynamic kidney scintigraphy, there was a lack of function of the left kidney. The right kidney was visualized in the typical place, with clear contours and normal sizes. The accumulation of the radiopharmaceutical substance is normal, the glomerular filtration process and the evacuation of the radiopharmaceutical being within normal range (fig. 4).

Discussions. NB was first described in 1864 by Rudolf Ludwig Karl Virchow, who called it "infantile glioma", later in 1891 the German pathologist Felix Marchand found that this neoplasm originates from the sympathetic nervous system and adrenal glands. The stage IV-S of neuroblastoma, which is characterized by liver metastases without bone metastases, was described in 1901 by William Pepper. Only in 1910 that James Homer Wright has used the term of "neuroblastoma", mentioning that some retroperitoneal and posterior mediastinal tumors are morphopathologically similar to immature primitive nerve tissue. [53]

Neuroblastoma usually presents as a solid tumor mass and rarely as a cystic lesion, the latter being located almost exclusively in the adrenal gland and very rarely found in other regions [45]. Molecular and biological investigations found several distinct subtypes of neuroblastoma with genetic changes in MYCN, ALK, PHOX2, PTPN11, ATRX, NRAS, etc. [22].

In 1971, Evans et al. proposed a classification of neuroblastoma in children based on the degree of spread of the neoplastic process, with the stages I, II, III, IV and IV-S [10].

According to the international neuroblastoma staging system (INSS, 1986), 4 clinical stages are distinguished depending on the results of the surgery [29].

Stage I - localized tumor located in the initial area of development; the neoplasm can be completely surgically removed with or without residual microscopic signs; macroscopic - the absence of lymph node involvement on both sides of the spine is confirmed.

Stage 2-A - unilateral tumor with removal of most of the tumor; microscopic - absence of bilateral lymph node involvement.

Stage 2-B - unilateral tumor, completely or mostly removed microscopic - unilateral lesion of the lymph nodes.

Stage 3 - the tumor is spread contralaterally with or without metastatic lesions of the regional lymph nodes; unilateral tumor with metastases in the contralateral lymph nodes; median tumor with metastases in bilateral lymph nodes.

Stage 4 - disseminated tumor with metastases in distant lymph nodes, bone, liver and bone marrow metastases.

Stage 4S (special), described by D'Angio et al. (1971), relates to patients with localized primary tumor in stage I, IIA and IIB but with liver metastases, skin and / or bone marrow [3, 53]. Neuroblastoma in stage IV-S, is

characterized by a comparatively favorable evolution of the disease, with a high rate of spontaneous tumor regression [38].

In 2009, the International Neuroblastoma Risk Group Staging System (INRGSS), developed by a consortium from North America, Europe, Japan and Australia, is based on a preoperative assessment of certain risk factors, according to which are distinguished: *L1 stage* - localized tumor that does not involve the vital structures indicated in the list of imagistically defined risk factors and limited to a single compartment of the body; *L2 stage* - locoregional tumor with the presence of one or more imagistically defined risk factors; *M stage* - distant metastatic disease (except stage MS); *MS stage* - metastatic disease in children under 18 months with metastases in liver, skin, and / or bone marrow [29].

According to Monclair T. et al. (2009) the imagistically defined risk factors in neuroblastic tumors are:

• *Ipsilateral tumor spread inside two compartments of the body*

- Neck-chest, thorax-abdomen, abdomen-pelvis;

• *Neck*

- Tumor involving the carotid and / or vertebral artery and / or the internal jugular vein;
- Tumor that extends to the base of the skull;
- Tumor that compresses the trachea;

• *Cervico-thoracic junction*

- Tumor involving the roots of the brachial plexus;
- Tumor involving the subclavian vessels and / or the vertebral and / or the carotid artery;
- Tumor that compresses the trachea;

• *Chest*

- Tumor covering the aorta and / or major branches;
- Tumor that compresses the trachea and / or main bronchi;
- Inferior mediastinal tumor with infiltration of the costo-vertebral junction between T9 and T12;

• *Thoraco-abdominal location*

- Tumor covering the aorta and / or vena cava;

• *Abdominal-pelvic location*

- Tumor with infiltrative growth in the hepatic hilum and / or hepatoduodenal ligament;
- Tumor involving branches of the superior mesenteric artery at the level of the mesenteric root;
- Tumor involving the celiac axis and / or the superior mesenteric artery;
- Tumor that invades one or both kidney pedicles;
- Tumor covering the aorta and / or vena cava;
- Tumor covering the iliac vessels;
- Pelvic tumor covering the iliac vessels;
- Pelvic tumor that crosses the sciatic notch;

• *Intraspinal tumor extension regardless of location, provided:*

- More than one third of the axial spinal canal is invaded and / or the perimedullary leptomeningeal spaces are not visible and / or the spinal cord signal is abnormal;

• *Infiltration of adjacent organs / structures:*

- Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block and mesentery;

• *Conditions that must be recorded, but which are not considered imagistically defined risk factors:*

- Multifocal primary tumors;
- Presence of pleural fluid, with or without malignant cells;
- Ascites, with or without malignant cells.

Neuroblastoma patients are stratified into very low, low, intermediate, and high-risk groups according to age, imagistically defined risk factors, and tumor biology, including: tumor histology, DNA ploidy, MYCN gene amplification, and chromosome 11q changes, treatment strategies being largely adapted to these groups [11, 32]. It should be noted that the presence of MYCN oncogenic amplification, observed in 20-30% of primary neuroblastoma cases, is a key factor in the INRG (International Neuroblastoma Risk Group) system that designates the high risk neuroblastoma, being one of the main indicators of tumor aggression, resistance to chemotherapy and a poor prognosis [39, 53]. The favorable and unfavorable histological subtypes of neuroblastoma are based on the level of Schwanian stroma present in the tumor, the mitosis-karyorexia index and the patient's age [13, 41].

The factors that determine a *favorable prognosis* are: the patient's age under 1 year, stage I, II or IVS, the absence of MYCN gene amplification and chromosomal segmental aberrations, polysomy. Factors of an *intermediate prognosis* include: the patient's age over 1 year, localized tumor with lymph nodes involvement, bone and bone marrow metastases in children under 1 year, absence of MYCN gene amplification and chromosomal segmental aberrations. *Poor prognosis* of the disease is determined by: patient age over 1 year, bone and bone marrow metastases, chromosomal segmental aberrations, such as deletions of the subtelomeric region (dellp36), long arm of chromosome 11 (del11q), enlargement of the long arm of chromosome 17 (+ 17q), amplification of the MYCN gene, morphologically undifferentiated tumor, high mitotic index [53].

Neuroblastoma treatment strategies include a combination of surgical treatment with chemotherapy, radiotherapy, myeloablative therapy, immunotherapy, stem cell use, therapeutic solutions being based on the stage of the disease, the patient's age, risk groups, etc. [7, 9, 33, 51]. Surgical resection of neuroblastoma has been shown to be effective in most low-risk cases, for intermediate-risk neuroblastoma the goal of surgery is to remove as much of the primary tumor as possible, surgical treatment being associated with pre- and postoperative chemotherapy [7, 18, 34, 49]. A

controversial issue is the role of surgical resection of the primary tumor and regional lymph nodes in patients with high-risk neuroblastoma [6, 8, 23]. Most authors emphasize the importance of resection in favor of a radical operation [8, 12, 48], some authors recommending in these cases the administration of chemotherapy before surgical resection, afterwards - the myeloablative chemotherapy [35, 36].

Surgical treatment of NB, in young children especially, presents significant risks, the rate of postoperative complications being up to 20-29%, and after repeated operations this index is 62.5% [15, 43, 50]. The literature describes postoperative renal atrophy as a complication after neuroblatom resection in children [19, 28, 50], which can have several causes, including: direct injury by kidney invasion, compression of renal vessels or ureter, spasm of renal vessels [37]. Some authors believe that dislocation of the renal artery may cause its spasm, and endothelial lesions may contribute to the stasis of renal blood flow with subsequent thrombosis of the renal artery [40, 47]. The development of renal atrophy is described even in cases of complete separation of renal vessels from the tumor, in order to reduce renal impairment being performed intraoperative monitoring of central venous pressure and urine flow, intravenous administration of electrolyte solutions, mannitol and furosemide, as well as the local application of lidocaine on the renal vessels, measures that can effectively contribute to the prevention of renal damage caused by renal vascular spasm [25]. It has been found that "tumor contact with renal vessels" is a major risk factor for the development of complications related to renal vessels, including renal atrophy [50]. It also needs to consider the nephrotoxic effect of chemotherapy and radiotherapy [42, 44], which in some cases may contribute to renal artery stenosis [2].

Conclusion.

Radical surgery followed by chemotherapy provides a beneficial local control in poorly differentiated retroperitoneal neuroblastoma with metastases in the regional lymph nodes in a child over 18 months of age. In cases of radical resection of a major retroperitoneal neuroblastoma, there is a risk of developing postoperative renal complications, including renal atrophy. Dislocation of the kidney with tumor compression of the renal hilum, including the renal vessels, may be considered a predictive risk factor for the development of ipsilateral postoperative renal atrophy in children with major retroperitoneal neuroblastoma.

REFERENCES

1. Abu-Arja R., Hashem H., El-Sheikh A., Abusin G. Neuroblastoma in monozygotic twins with distinct presentation pathology and outcome: is it familial or in utero metastasis. Pediatr. Blood Cancer. 2014. 61:1124-5.
2. Beckham T.H., Casey D.L., La Quaglia M.P., Kushner B.H., Modak S., Wolden S.L. Renal function outcomes of high-risk neuroblastoma patients undergoing radiation therapy. Int. J. Radiation Oncol. Biol. Phys. 2017. 99(2):486-93.
3. Bernardi B., Di Cataldo A., Garaventa A., Massirio P., Viscardi E. et al. Stage 4S neuroblastoma: features, management and outcome of 268 cases from the Italian Neuroblastoma Registry. Italian J. Pediatr. 2019. 45:8. https://doi.org/10.1186/s13052-018-0599-1.
4. Borriello L., Seeger R.C., Asgharzadeh S., DeClerck Y.A. More than the genes, the tumor microenvironment in neuroblastoma. Cancer Letter. 2016. 380:304-14.
5. Campagna G., Rosenfeld E., Foster J., Vasudevan S., Nuchtern J. et al. Evolving biopsy techniques for the diagnosis of neuroblastoma in children. J. Pediatr. Surg. 2018; 53:2235-9.
6. Dubbers M., Simon T., Berthold F., Fischer J., Volland R. et al. Retrospective analysis of relapsed abdominal high-risk neuroblastoma. J. Pediatr. Surg. 2018. 53:558-66.
7. Dumba M., Jawad N., McHugh K. Neuroblastoma and nephroblastoma: a radiological review. Cancer Imaging. 2015. 15:5. DOI 10.1186/s40644-015-0040-6.
8. Englum B.R., Rialon K.L., Speicher P.J., Gulack B., Driscoll T.A. et al. Value of surgical resection in children with higj-risk neuroblastoma. Pediatr. Blood Cancer. 2015. 62:1529-35.
9. Esposito M.R., Aveic S., Seydel A., Tonini G.P. Neuroblastoma treatment in the post-genomic era. J. Biomed. Sci. 2017. 24:14. DOI 10.1186/s12929-017-0319-y.
10. Evans A.E., D'Angio G.J., Randolph J. A proposed staging for children with neuroblastoma. Children's cancer study group A. Cancer. 1971. 27(2):374-8.
11. Fahy A.S., Roberts A., Nasr A., Irwin M.S., Gerstle J.T. Long term outcomes after concurrent ipsilateral nephrectomy versus kidney-sparing surgery for high-risk, intraabdominal neuroblastoma. J. Pediatr. Surg. 2019. 54:1632-7.
12. Fischer J., Poh A., Volland R., Hero B., Dubbers M. et al. Complete surgical improves outcome in INRG high-risk patients with localized neuroblastoma older than 18 monts. BMC Cancer. 2017. 17:520. DOI 10.1186/s12885-017-3493-0.
13. Fukudome N., Kimura F., Arita S., Atupelage C., Mizuguchi K. Significance of cytological findings of neuroblastomas: rosette arrangement and neuropil structure. J. Cytol. Histol. 2015. 6: 357. doi:10.4172/2157-7099.1000357.

14. Fusaro F., Cecchetto G., Boglino C., Inserra A., Zanon G.F. et al. Measures to prevent renal impairment after resection of retroperitoneal neuroblastoma. Pediatr. Surg. Int. 2002. 18: 388-91.
15. Gunther P., Holland-Cunz S., Schupp C.J., Stockklausner C., Hinz U., Schenk J.P. Signifi cance of image-defined risk factors for surgical complications in patients with abdominal neuroblastoma. Eur. J. Pediatr. Surg. 2011. 21:314-7.
16. Hassan S.F., Mathur S., Magliaro T.J., Larimer E.L., Ferrell L.B. et al. Needle core vs open biopsy for diagnosis of intermediate- and high-risc neuroblastoma in children. J. Pediatr. Surg. 2012; 47:1261-6.
17. Holub J.L., Qiu Y.Y., Chu F., Madonna M.B. The role of nerve growth factor in caspase-dependent apoptosis in human BE (2) C neuroblastoma. J. Pediatr. Surg. 2011; 46:1191-6.
18. Iehara T., Yagyu S., Tsuchiya K., Kuwahara Y., Miyachi M. et al. Residual tumor in cases of intermediate-risk neuroblastoma did not influence the prognosis. Jpn. J. Clin. Oncol. 2016. 46(7):661-6.
19. Iehara T., Yoneda A., Yokota I., Takahashi H., Teramukai S. et al. Results of a prospective clinical trial JN-L-10 using image-defined risk factors to inform surgical decisions for children with low-risk neuroblastoma disease: a report from the Japan Children's Cancer Group Neuroblastoma Committee. Pediatr. Blood Cancer. 2019. e27914. https://doi.org/10.1002/pbc.27914.
20. Kandula S., Sutter A., Prabhu R.S., Jegadeesh N., Esiashvili N. Reassessing dose constraints of organs at risk in children with abdominal neuroblastoma treated with definitive radiation therapy: A correlation with late toxicity. Pediatr. Blood Cancer. 2015. 62(6):970-5.
21. Kubota M., Yagi M., Kanada S., Okuyama N., Kinoshita Y. et al. Long-term follow-up status of patients with neuroblastoma after undergoing either aggressive surgery or chemotherapy - a single institutional study. J. Pediatr. Surg. 2004. 39(9):1328-32.
22. Kurihara S., Hiyama E., Onitake Y., Yamaoka E., Hiyama K. Clinical features of ATRX or DAXX mutated neuroblastoma. J. Pediatr. Surg. 2014. 49:1835-8.
23. La Quaglia M.P. State of the art in oncology: High risk neuroblastoma, alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, and POST-TEXT 3 and 4 hepatoblastoma. J. Pediatr. Surg. 2014. 49:233-40.
24. Lautz T.B., Naiditch J.A., Clark S., Chu F., Madonna M.B. Efficacy of class I and II vs class III histone deacetylase inhibitors in neuroblastoma. J. Pediatr. Surg. 2012. 47:1267-71.
25. Liu Z.L., Xiao Y.H., Chen D.X., Wang Z. The impact of gross total resection on survival in children with stage III/IV neuroblastoma – study of clinical efficacy in 21 cases. Eur. J. Med. Pharmacol. Sci. 2014. 18:2253-7.
26. Luo Y.B., Cui X.C., Yang L., Zhang D., Wang J.X. Advances in the surgical treatment of neuroblastoma. Chin. Med. J. 2018. 131(19)2332-7.
27. Manjunath S., Mouli S., Singh K.R., Rana C., Ramakant P., Mishra A. Neuroblastoma in late adolescence: case report and review of literature. World J. Endoc. Surg. 2018. 10(3):157-62.
28. Mohamed A.H.A., Mahmoud I.H., El Dein H.M.S., Sallam K.R., Wahba H.S. Assessment of the validity of imagedefined risk factors (IDRFs) in abdominal neuroblastoma Egyptian J. Radiol. Nuclear Med. 2020. 51:88. https://doi.org/10.1186/s43055-020-00205-2.
29. Monclair T., Brodeur G.M., Ambros P.F., Brisse H.J., Ceccheto G. et al. The International Neuroblastoma Risk Group (INRG) Staging System: An INRG task force report. J. Clin. Oncol. 2009. 27(2):298-303.
30. Nakaoka T., Uemura S., Nakagawa Y., Yano T., Oda M. Retroperitoneal ganglioneuroblastoma resected 8 years after mass screening: a case report. J. Pediatr. Surg. 2007. 42:E29-E32.
31. Ogura T., Hiyama E., Kamei N., Kamimatsuse A., Ueda Y., Ogura K. Clinical feature of anaplastic lymphoma kinase-mutated neuroblastoma. J. Pediatr. Surg. 2012. 47:1789-96.
32. Phelps H.M., Ndolo J.M., Van Arendonk K.J., Chen H., Dietrich H.L. et al. Association between image-defined risk factors and neuroblastoma outcomes. J. Pediatr. Surg. 2019. 54:1184-91.
33. Pinto N.R., Applebaum M.A., Volchenbaum S.L., Matthay K.K., London W.B. et al. Advances in risc classification and treatment strategies for neuroblastoma. J. Clin. Oncol. 2015. 33(27):3008-17.
34. Qin H., Yang S., Cai S., Ren Q., Han W. et al. Clinical characteristics and risk factors of 47 cases with ruptured neuroblastoma in children. BMC Cancer. 2020. 20:243. https://doi.org/10.1186/s12885-020-06720-9.
35. Rojas Y., Jaramillo S., Lyons K., Mahmood N., Wu M.F. et al. The optimal timing of surgical resection in high-risk neuroblastoma. J. Pediatr. Surg. 2016. 51:1665-9.
36. Simon T., Häberle B., Hero B., von Schweinitz D., Berthold F. Role of surgery in the treatment of patients with stage 4 neuroblastoma age 18 months or older at diagnosis. J. Clin. Oncol. 2013. 31(6):752-8. DOI:10.1200/ JCO.2012.45.9339.
37. Tanabe M., Otinuma N., Iwai J., Yoshida H., Takahash H. Renal impairment after surgical resection of neuroblastoma. J. Pediatr. Surg. 1996. 31(9):1252-5.
38. Tas M.L., Nagtegaal M., Kraal K., Tytgat G., Abeling N. Et al. Neuroblastoma stage 4S: tumor regresion rate and risk factors of progressive disease. Pediatr. Blood Cancer. 2019. e28061. https://doi.org/10.1002/pbc.28061.
39. Taylor J.S., Zeki J., Ornell K., Coburn J., Shimada H. et al. Down-regulation of MYCN protein by CX-5461 leads to neuroblastoma tumor growth suppression. J. Pediatr. Surg. 2019. 54:1192-7.
40. Tokiwa K., Fumino S., Ono S., Iwai N. Results of retroperitoneal lymphadenectomy in the treatment of abdominal neuroblastoma. Arch. Surg. 2003. 138(7):711-5.
41. Van Arendonj K.J., Chung D.H. Neuroblastoma: tumor biology and its implications for staging and treatment. Children. 2019. 6:12. DOI: 10.3390/children6010012.

42. Vollmer K., Gfroerer S., Theilen T.M., Bochennek K., Klingebiel T. et al. Radical surgery improves survival in patients with stage 4 neuroblastoma. World J. Surg. 2018. 42(6):1877-84.
43. Von Allmena D., Grupp S., Diller L., Marcus K., Ecklund K. et al. Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. J. Pediatr. Surg. 2005. 40:936-41.
44. Warmann S.W., Seitz G., Schaefer J.F., Scheel-Walter H.G., Leuschner I., Fuchs J. Vascular encasements as element of risk stratification in abdominal neuroblastoma. Surg. Onco. 2011. 20:231-5.
45. Watanabe M., Komuro H., Kaneko M., Hori T., Tatekawa Y. et al. A rare case of presacral cystic neuroblastoma in an infant. J. Pediatr. Surg. 2008. 43:1376-9.
46. Wu X.L., Dai Y.J., Sun G.Y., Wang L.K., Han L. et al. Adult neuroblastoma in the retroperitoneum: a case report. Medicine (Baltimore). 2018. 97(51):e13750. doi: 10.1097/MD.0000000000013750.
47. Yamagiwa I., Obata K., Saito H., Washio M. Renal atrophy following removal of a neuroblastoma. Pediatr. Surg. Int. 1994. 9:387-90.
48. Yang X., Chen J., Wang N., Liu Z., Li F. et al. Impact of extent of resection on survival in high-risk neuroblastoma: a systematic review and meta-analysis. J.Pediatr. Surg. 2019. 54:1487-94.
49. Yeung F., Chung P.H.Y., Tam P.K.H., Wong K.K.Y. Is complete resection of high-risk stage IV neuroblastoma associated with better survival? J. Pediatr. Surg. 2015. 50:2107-11.
50. Yoneda A., Nishikawa N., Uehara S., Oue T., Usui N. et al. Can image-defined risk factors predict surgical complications in localized neuroblastoma? Eur.J. Pediatr. Surg. 2016. 26:177-22.
51. Zage P.E. Novel therapies for relapsed and refracrory neuroblastoma. Children. 2018. 5:148. DOI:10.3390/children5110148.
52. Качанов Д.Ю., Шаманская Т.В., Муфтахова Г.М., Варфоломеева С.Р. Нейробластома 4S стадии. Вопр. Гематол./Онкол. Иммунопатол. Педиатрии. 2014. 13(2):9-19.
53. Строганова А.М., Карселадзе А.И. Нейробластома: морфологическая структура, молекулярно-генетические особенности и прогностические факторы. Успехи молекулярной онкологии. 2016; 3(3):32-43.

Conflicts of interest: *authors have no conflict of interest to declare*