KISTER, Klaudia, LASKOWSKI, Jakub, BRONST, Paulina, MAZUR, Magdalena, MAŁOLEPSZA, Aleksandra, ZACH-ŹRÓDLAK, Monika, CZECHOWSKA, Julia, ROSA, Lidia, REKTOR, Natalia and SZABRAŃSKA, Anna. Update on Wilms tumor. Journal of Education, Health and Sport. 2023;46(1):453-467. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2023.46.01.031
https://apcz.umk.pl/JEHS/article/view/45369
https://zenodo.org/record/8290233

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 17.07.2023 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 17.07.2023 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 27.07.2023. Revised:21.08.2023. Accepted: 28.08.2023. Published: 31.08.2023.

Update on Wilms tumor

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Abstract

Background: Wilms' tumor is the most common childhood renal neoplasm. Among the worst prognosis forms are the bilateral form. The symptom complex is non-specific for malignancy; the first symptoms may include hypertension. Hematuria occurs in 30% of patients. The incidence of distant metastases at the time of diagnosis in children with Wilms' tumor is estimated to be about 20%.The purpose of this article is to present a review of the literature on the standardization of diagnosis, the latest treatment standards and to assess the prognosis of Wilms' Tumor.

Matherial and methods: Using PubMed, SCOPUS and Web of Science databases, the authors reviewed the peer-reviewed international literature from 1980-2023 using the keywords: "Wilms tumor," "renal tumor," "nephroblastoma."

Discussion: Bilateral tumors have the worst prognosis - according to the National Wilms Tumor Study Group, long-term survival is achieved in only 12% to 56% of patients. The prognosis of Wilms' tumor is also dependent on the occurrence of recurrences - local as well as localized outside the renal tissue. A factor directly affecting long-term survival is recurrence, mainly observed within 24 months after the end of therapy. The limitations of conventional therapies, including surgery, chemotherapy and radiotherapy, in preventing recurrence in WT patients and their potential to cause long-term side effects.

Conclusions:

Bilateral Wilms tumor is associated with more aggressive therapy than unilateral disease.In single kidney disease, therapeutic management is aimed at radical removal of all tumor foci, whereas in bilateral tumor, the goal of any management should additionally be to try to preserve the best possible renal function.

Screening in children is important in cancer. General physicians should refer patients for additional imaging studies when there are any diagnostic doubts, as cancer is characterized by a long, asymptomatic development.

Keywords :wilms tumor, renal tumor, nephroblastoma

1. Introduction

Wilms' tumor is the most common childhood renal neoplasm. In children, it accounts for about 6% of all cancers [1,2]. The prognosis of this disease depends on the degree of malignancy of the tumor and concomitant features, and long-term survival is achieved in favorable conditions by up to 90%. Among the worst prognosis forms are the bilateral form of Wilms tumor and the anaplastic form, which is characterized by aggressive growth. Wilms' tumor develops most often in children of early childhood, with a peak incidence at age 2. Males are slightly more commonly affected than females [3,4]. The bilateral form accounts for 6% of all new discoveries [5].

Wilms' tumor most often develops as an isolated form, but is rarely detected with the coexistence of congenital abnormalities of the kidney, among which are horseshoe kidney, renal dysplasia or cryptorchidism [9]. It is also accompanied by genetic syndromes such as Beckwith-Wiedeman syndrome or Denys-Drash syndrome [10]. Wilms' tumor in its early stages does not present a characteristic clinical picture. The symptom complex is non-specific for malignancy; the first symptoms may include hypertension. Hematuria occurs in 30% of

patients [11,12]. Early detection of cancer is difficult because it develops at an age when children are just acquiring the ability to speak and cannot accurately describe the symptoms that occur. Medical consultation depends on the vigilance of the parent. In addition, symptoms occurring that are non-specific to the tumor, such as subfebrile states, can easily be mistaken for infection, delaying the treatment process. Unlike the most commonly diagnosed childhood cancer - leukemia, here we do not find any typical deviations in blood results. Rarely, increases in calcium and adrenocorticotropic hormone levels are observed [13]. The picture presented can be difficult to diagnose for an inexperienced physician, so specialists alert for a multidisciplinary view of the patient.

The diagnosis of Wilms' tumor is based on abnormalities found on imaging studies. Basic tests include abdominal ultrasound, which can be performed in primary care offices. If there is any doubt about the identified imaging abnormalities, the patient should be referred to a higher referral center, where a CT or MRI scan of the abdomen will be performed. These form the basis of the diagnosis. MRI is the preferred method for cases of bilateral tumor [14]. During diagnostic procedures, it is important to keep in mind the possibility of developing tumors of other origin in the kidney than Wilms' Tumor. In children before the age of three months, congenital mesoblastic nephrosarcoma is much more common than Wilms' tumor. The proportions reverse as early as six months of age. An international study examined patients in the first months of life with kidney tumors. The results highlighted that one in three tumors had a cellular origin other than Wilms' Tumor. Others include rhabdomyosarcoma, renal carcinoma and others [15]. Renal lymphoma, which can also develop in the first months of life despite a later peak in incidence, should also be considered during the differential diagnosis.

The incidence of distant metastases at the time of diagnosis in children with Wilms' tumor is estimated to be about 20% [16]. The most common site of metastasis is considered to

be the lungs. The typical radiological lesion is a pleural effusion, which develops in the course of metastatic growth. Other metastatic destinations such as mediastinal lymph nodes and the liver are rare. The latter indicates a particularly poor prognosis. The presence of liver lesions reduces long-term survival rates to 60%, and a prerequisite for achieving the above result is the complete resection of all microscopic and macroscopic lesions [16]. Decisions on the selected treatment regimen depend on the stage of the lesion and the histopathological result [17]. Nephroblastoma stages are distinguished according to the local extent of the lesion, infiltration of surrounding tissues and the presence of distant metastases [18].

Cases with involvement of two kidneys account for 6% of all diagnosed tumors [16]. The bilateral form of nephroblastoma often develops as a result of genetic mutations and coexists with congenital syndromes [19].

Often, bilateral disease is defined by the presence of a tumor in one kidney and foci of nephroblastomatosis, i.e. the presence of primary renal tissue in the other kidney, or the presence of foci in both kidneys due to a questionable radiological picture.

The treatment of Wilms' tumor is one of the greatest successes of modern medicine. In the history of treatment, surgery has always been an integral part of the primary treatment of Wilms' tumor. During surgery, transperitoneal access is used [20], as a lateral incision is inappropriate for nephroblastoma. Before surgery, all adjacent abdominal organs, including the opposite kidney, should be carefully examined. Wilms' tumor is a well-circumscribed tumor, so it should be removed without disturbing the continuity of the capsule. It is crucial not to cause intraoperative tumor leakage, as this is associated with a worse prognosis [21]. Multimodal therapy, including surgery, radiotherapy and chemotherapy, constitutes the treatment regimen for Wilms' tumor. The not-so-distant addition and refinement of chemotherapy and radiotherapy has had a huge impact on achieving improved patient survival rates. Modern therapeutic regimens have minimized exposure to radiotherapy and attempt to

reduce the administration of anthracyclines, which are among the main factors associated with late side effects; they are still used as a first-line treatment regimen in high-grade tumors. It is extremely important to consider advances in the treatment of Wilms' tumor worldwide, as survival rates in underdeveloped countries are significantly lower compared to highly developed countries [22]. Obecnie wytyczne postępowania są różne w Europie i Ameryce, jednak oba pozwalają uzyskać satysfakcjonujące wyniki leczenia.

On the old continent, procedures are developed by the International Society of Pediatric Oncology (SIOP). The use of chemotherapy and further treatment depends on the patient's classification into a particular risk group. In Europe, the focus has been on preoperative chemotherapy, bearing in mind the risk of intraoperative interference. Specialists have developed a four-week regimen for administering preoperative chemotherapy, including actinomycin and vincristine for all patients six months and older with localized disease. If distant metastases are present, preoperative treatment is longer, lasting six weeks, and additionally includes the administration of doxorubicin [23]. Overall management depends on the clinical picture and stage of the disease.

The National Wilms Tumor Study Group (NWTSG) in the U.S. recommends preoperative chemotherapy during Wilms tumor treatment only in special cases, such as bilateral tumor form or in cases of intratumoral proliferations typical in 5% of cases. The third and final indication is so-called inoperable tumors - large, diffuse tumors involving vital structures, the resection of which is associated with serious consequences, as well as loss of life [24]. W większości pozostałych przypadków guza Wilmsa protokoły opracowane przez NWTSG zalecają najpierw wykonanie nefrektomii, a dopiero następnie chemioterapii dostosowanej do stopnia zaawansowania guza [25]. Despite the different treatment regimens, overall event-free survival is similar in patient groups treated according to both European and American protocols [26], and is currently 85-90%, using multimodality therapy [27].

The purpose of this article is to present a review of the literature on the standardization of diagnosis, the latest treatment standards and to assess the prognosis of Wilms' Tumor.

2. Material and methods: Using PubMed, SCOPUS and Web of Science databases, the authors reviewed the peer-reviewed international literature from 1980-2023 using the keywords: "Wilms tumor," "renal tumor," "nephroblastoma." Articles originally written in a language other than English were not considered. Finally, 41 articles were included in the review.

3. Discussion

Wilms' tumor is one of the better prognostic cancers of childhood. The best results are achieved in patients with tumor diagnosed at stages I and II. More than 95% cure rates are achieved in this group [28]. Tumors in stage III and IV have a slightly worse prognosis - 75% and 65%, respectively [29,30]. Bilateral tumors have the worst prognosis - according to the National Wilms Tumor Study Group, long-term survival is achieved in only 12% to 56% of patients [31,32]. A factor of key prognostic importance in patients with Wilms tumor is early diagnosis and initiation of treatment. A study by Pritchard-Jones et al [33] showed differences between the German and British health systems in the diagnosis of renal tumors in children, which directly translated into cure rates in patients. In the British health system, the primary medical representative was the family doctor, while in Germany children were consulted by qualified pediatricians. The study found that in Germany, tumors were diagnosed more quickly, at an early stage of development, compared to the UK, where a higher percentage of children had tumors diagnosed later, at a higher stage. In Germany, a higher proportion of tumors were detected incidentally, before clinical symptoms developed. By contrast, in the UK, tumors were more often detected in conjunction with the onset of complaints. A 3% difference in the rate of achieving long-term event-free survival was found between the countries studied.

The prognosis of Wilms' tumor is also dependent on the occurrence of recurrences - local as well as localized outside the renal tissue. A factor directly affecting long-term survival is recurrence, mainly observed within 24 months after the end of therapy [34]. After a long period of observation, recurrence of the disease is sporadic. If it does occur, it drastically worsens the prognosis. Disease free survival is achieved at 50% of patients. This problem mainly affects the lungs, kidneys in the case of sparing surgery and, less frequently, the liver [35]. The last location is characterized by the worst results of therapy [36,37]. The limitations of conventional therapies, including surgery, chemotherapy and radiotherapy, in preventing recurrence in WT patients and their potential to cause long-term side effects, necessitate the use of new therapeutic strategies, such as immunotherapy, in this disease [38].

Because of the risk of recurrence, patients should remain under continuous specialized follow-up after treatment. Patients should have regular radiological follow-up, as CT imaging is the first-line test for detecting recurrence [39].

From the analysis of the above data, it appears that many factors influence the outcome of children with Wilms tumor. Another prognostically important factor in children with bilateral Wilms tumor is the individually determined treatment plan [40]. While the choice of chemotherapy regimen is dictated by the current therapeutic protocol, the decision on surgical treatment, its extent and technique, should be made very prudently [41].

4. Conclusions:

Bilateral Wilms tumor is associated with more aggressive therapy than unilateral disease.In single kidney disease, therapeutic management is aimed at radical removal of all tumor foci, whereas in bilateral tumor, the goal of any management should additionally be to try to preserve the best possible renal function.

Radical nephrectomy is associated with maximizing the chances of long-term disease-free survival, but renal tissue-sparing surgery should be the goal in the treatment of bilateral

lesions. Such a procedure reduces the development of premature renal failure associated with the need for renal replacement therapy, which significantly impairs quality of life.

The success of treatment is highly dependent on the detection of lesions at an early stage of development. This avoids additional treatment regimens that are aggressive to the body and results in better therapeutic outcomes. Screening in children is important in cancer, so the need for frequent screening when symptoms are unclear is emphasized. Family physicians should refer patients for additional imaging studies when there are any diagnostic doubts, as cancer is characterized by a long, asymptomatic development.

5. Data

Author's contribution:

Conceptualization: Magdalena M., Klaudia K. Jakub L.; Methodology: Magdalena M., Klaudia K.; Software: Jakub L.; Check: Aleksandra M., Natalia R.; Formal analysis: Paulina B.; Investigation: Anna S.; Resources: Magdalena M. Jakub L.;Data curation: Magdalena M.; Writing - rough preparation: Magdalena M., Julia C.; Writing - review and editing: Magdalena M., Lidia R. Jakub L; Visualization: Monika Z.; Supervision: Magdalena M.; Project administration: Magdalena M., Jakub L.

All authors have read and agreed with the published version of the manuscript.

Funding Statement: No funding received.

Institutional Review Board Statment: Not applicable.

Informed Consent Statment: not considered

Data Availability Statement: The data presented in this study are avaliable on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gratias EJ, Dome JS, Jennings LJ, Chi YY, Tian J, Anderson J et al. Association of Chromosome 1q Gain With Inferior Survival in Favorable-Histology Wilms Tumor: A Report From the Children's Oncology Group. J. Clin. Oncol. 2016;34(26):3189–94.

2. Irtan S, Ehrlich PF, Pritchard-Jones K. Wilms tumor: "State-of-the-art" update. Semin Pediatr Surg. 2016;25(5):250–6.
3. Termuhlen AM, Tersak JM, Liu Q, Yasui Y, Stovall M, Weathers R, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. Pediatr. Blood Cancer. 2011;57(7):1210–6.
4. Wong KF, Reulen RC, Winter DL, Guha J, Fidler MM, Kelly J, et al. Risk of Adverse Health and Social Outcomes Up to 50 Years After Wilms Tumor: The British Childhood Cancer Survivor Study. J. Clin. Oncol. 2016;34(15):1772–9.
5. Bernstein L, Linet M, Smith MA, Olshan AF. Cancer incidence and survival among children and adolescents. National Cancer Institute. SEER Program. Bethesda. NIH. 1999;99(4649):79–90.
6. Kramer S, Meadows AT, Jarrett P. Racial variation in incide nce of Wilms` tumor: relationship to congenital anomalies. Med. Pediatr. Oncol. 1984;12:401–405.
7. Aydın B, Akyüz C, Yalçın B, Ekinci S, Oğuz B, Akçören Z et al. Bilateral Wilms tumors: Treatment results from a single center. Turk. J. Pediatr. 2019;61(1):44-51.
8. Paya K, Horcher E, Lawrenz K, Rebhandl W, Zoubek A. Bilateral Wilms' tumor--surgical aspects. Eur. J. Pediatr. Surg. 2001;11(2):99-104.
9. Pendergrass TW. Congenital anomalies in children with Wilms' tumor: a new survey. Cancer. 1976;37(1):403-8.
10. Shuman C, Kalish JM, Weksberg R. Beckwith-Wiedemann Syndrome. Seattle (WA): University of Washington. Seattle. 2023.
11. Green DM. The diagnosis and management of Wilms' tumor. Pediatr. Clin. North. Am. 1985;32(3):735-54.
12. Vujanić GM, Sandstedt B, Harms D, Kelsey A, Leuschner I, de Kraker J. Nephroblastoma Scientific Committee. Revised International Society of Paediatric

Oncology (SIOP) working classification of renal tumors of childhood. Med. Pediatr. Oncol. 2002;38(2):79-82.

13. Granger J, Gidvani VK. Acquired factor VII deficiency associated with Wilms tumor. Pediatr. Blood. Cancer. 2009;52(3):394-5.
14. Servaes SE, Hoffer FA, Smith EA, Khanna G. Imaging of Wilms tumor: an update. Pediatr. Radiol. 2019;49(11):1441-1452.
15. Fogelström A, Caldeman C, Wester T, Löf Granström A, Mesas Burgos C. Prevalence of Beckwith Wiedemann Syndrome and Risk of Embryonal Tumors in Children Born with Omphalocele. J. Pediatr. Surg. 2023;31:0022-3468.
16. Ehrlich PF, Ferrer FA, Ritchey ML, Anderson JR, Green DM, Grundy PE et al. Hepatic metastasis at diagnosis in patients with Wilms tumor is not an independent adverse prognostic factor for stage IV Wilms tumor: a report from the Children's Oncology Group/National Wilms Tumor Study Group. Ann. Surg. 2009;250(4):642-8.
17. Li T, Wang H, Chen X, He L. Case report: The CT features of pediatric retroperitoneal extrarenal Wilms tumor: a report of two cases and literature review. Front Pediatr. 2023;11:1161603.
18. Liu B, Abraham N, Chitsike I, Sylvie CGL, Kambugu J, Stévy NMA et al. Enhancing information on stage at diagnosis for childhood cancer in Africa. Pediatr. Blood Cancer. 2023:30555.
19. Coppes MJ, de Kraker J, van Dijken PJ, Perry HJ, Delemarre JF, Tournade MF et al. Bilateral Wilms' tumor: long-term survival and some epidemiological features. J. Clin. Oncol. 1989;7(3):310-5.
20. Kim S, Chung DH. Pediatric solid malignancies: neuroblastoma and Wilms' tumor. Surg. Clin. North. Am. 2006;86(2):469-87.

21. National Wilms 'Tumor Study Committee. Wilms' tumor: status report. J. Clin. Oncol. 1991;9:877–887.
22. Zahir M, Alidousti A, Kajbafzadeh AM, Arshadi H, Kompani F, Hajivalizadeh S et al. Current status and future perspectives of wilms tumor treatment in Iran. Ann. Med. Surg. (Lond). 2023;85(5):1425-1429.
23. Godzinski J. The current status of treatment of Wilms' tumor as per the SIOP trials. J. Indian Assoc. Pediatr. Surg. 2015;20(1):16-20.
24. Israels T. Wilms tumor in Africa: challenges to cure. Pediatr. Blood Cancer. 2012;58(1):3-4.
25. Chui CH. Editorial: Recent advances in organ-sparing techniques in pediatric solid tumor surgery. Front Pediatr. 2023;11:1247287.
26. Sonn G, Shortliffe LM. Management of Wilms tumor: current standard of care. Nat. Clin. Pract. Urol. 2008;5(10):551-60.
27. Israels T. Wilms tumor in Africa: challenges to cure. Pediatr. Blood Cancer. 2012;58(1):3-4.
28. Saltzman AF. Cost NG, Romao RLP. Wilms Tumor. Urol. Clin. North Am. 2023;50(3):455-464.
29. Szavay P, Luithle T, Garf N, Furtwangler R, Fuchs J. Primary hepatic metastases in nephroblastoma - a report of the SIOP / GPOH study. J. Pediatr. Surg. 2006;41:168–172.
30. Varan A. Wilms' tumor in children: an overview. Nephron. Clin. Pract. 2008;108(2):83-90.
31. Breslow NE, Collins AJ, Ritchey ML, Grigoriev YA, Peterson SM, Green DM. End stage renal disease in patients with Wilms tumor: results from the National Wilms

Tumor Study Group and the United States Renal Data System. J. Urol. 2005;174(5):1972-5.

32. Rudin C. Pritchard J. Fernando ON. Duffy PG. Trompeter RS. Renal transplantation in the management of bilateral Wilms 'tumor (BWT) and of Denys – Drash syndrome (DDS). Nephrol. Dial. Transplant. 1998;13(6):1506–1510.
33. Ertan S, Ehrlich PF, Pritchard-Jones K. Wilms tumor: "State-of-the-art" update. Semin. Pediatr. Surg. 2016;25(5):250-256.
34. Brok J, Lopez-Yurda M, Tinteren HV, et al. Relapse of Wilms 'tumor and detection methods: a retrospective analysis of the 2001 Renal Tumor Study Group - International Society of Pediatric Oncology Wilms' Tumor Protocol Database. Lancet Oncol. 2018;19:1072–1081.
35. Grundy P, Breslow N, Green DM, Sharples K, Evans A, D'Angio GJ. Prognostic factors for children with recurrent Wilms' tumor: results from the Second and Third National Wilms' Tumor Study. J. Clin. Oncol. 1989;7(5):638-47.
36. Szavay P, Luithle T, Garf N, Furtwangler R, Fuchs J. Primary hepatic metastases in nephroblastoma - a report of the SIOP / GPOH study. J. Pediatr. Surg. 2006;41:168–172.
37. Varan A. Wilms' tumor in children: an overview. Nephron. Clin. Pract. 2008;108(2):83-90.
38. Sanatkar SA, Heidari A, Arya S, Ghasemi M, Rezaei N. The potential role of immunotherapy in Wilms' tumor: opportunities and challenges. Curr Pharm Des. 2023:21.
39. Jha SK, Brown C, Kang L, Diaz ES, Gwal K, Alvarez E et al. Update on the Role of Imaging in Staging of Common Pediatric Abdominal Tumors. Curr. Probl. Cancer. 2023;47(2):100969.

40. Chen SY, Lee WG, Laifman E, Mack SJ, Zhou S, Kim ES. A Single Center Experience With Bilateral Wilms Tumor. Am Surg. 2023;19:31348231175446.

41. Leslie SW, Sajjad H, Murphy PB. Wilms Tumor. In: StatPearls [Internet]. Treasure Island (FL): 2023.