DIAGNOSIS AND MANAGEMENT OF WILMS TUMOR IN CHILDREN

Diagnóstico e manejo do Tumor de Wilms na população infantil

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ABSTRACT

Wilms tumor (WT), or nephroblastoma, is a malignant embryonic abnormality of the mesodermal lineage mostly identified during childhood. Initially, the clinical sign is an asymptomatic abdominal mass with subtle appearance. **Objective:** to analyze the diagnostic method and treatment of WT in children. Methods: an integrative review was conducted in Medline, Portal de Periódicos CAPES, Lilacs, and Scopus databases. The search was performed from March 1 to May 20, 2022 using the descriptors "*Tumor de Wilms*", "*Nefroblastoma*", "*Diagnóstico*", and "*Tratamento"*. Inclusion criteria considered publications from the last five years written in Portuguese English, and Spanish. **Results and discussion:** a total of 20 studies were selected and included in the discussion: 70% were retrieved from CAPES Periodicals, 5% from Medline, 15% from Lilacs, and 10% from the Scopus database. To ensure safe and effective diagnosis, studies used protocols from the International Society of Pediatric Oncology and guidelines from the Child Oncology Group. Although a positive prognosis was observed in most cases, it might be affected by the histological stratification of the tumor and the treatment onset period. **Conclusion:** The multidisciplinary team was crucial for early diagnosis, which directly affects treatment efficacy. Also, results from imaging and immunohistology are essential to tumor stratification and therapy adjustment.

Keywords: Wilms Tumor, Diagnosis, Therapeutics, Pediatrics.

RESUMO

O tumor de Wilms (TW), também conhecido como nefroblastoma, é uma alteração embrionária maligna da linhagem mesodérmica identificada predominantemente ao longo da infância. A apresentação clínica inicial mais comum é sutil e cursa com o surgimento de uma massa abdominal assintomática. **Objetivo**: Analisar a abordagem de diagnóstico e tratamento do TW em crianças. **Método**: Tratou-se de uma revisão integrativa realizada nas bases de dados Portal Periódicos CAPES, Medline, Lilacs e Scopus, em artigos com os descritores "Tumor de Wilms", "Nefroblastoma", "Diagnóstico" e "Tratamento", no período entre 01 de março e 20 de maio, 2022. Filtros de busca adotados: estudos em português, inglês e espanhol publicados nos últimos 5 anos. No total, 20 artigos foram incluídos. **Resultados e discussão**: Do total de artigos selecionados, 70% são procedentes da CAPES, 5% da Medline, 15% da Lilacs e 10% da Scopus. Os autores estão em consonância quanto à adoção de protocolos como o do *International Society of Paediatric Oncology* e as diretrizes do *Children's Oncology Group* para a definição segura e eficaz do diagnóstico. O prognóstico permanece positivo na maioria dos casos. No entanto, algumas variáveis podem influenciar a evolução, como o tipo histológico do tumor e o período de início do tratamento. **Conclusão**: A atenção da equipe multidisciplinar no processo de diagnóstico precoce influencia diretamente na qualidade do tratamento prestado ao paciente. O resultado de exames de imagem e a avaliação imuno-histológica são essenciais ao estadiamento e à adequação terapêutica.

Palavras-chave: Tumor de Wilms; Nefroblastoma; Diagnóstico; Tratamento; Pediatria.

INTRODUCTION

Wilms tumor (WT), or nephroblastoma, is the most prevalent abdominal neoplasm during childhood, representing about 90% of renal cancers in children. Despite the restricted access to specialized services, low socioeconomic conditions, and tumor severity, survival rates in developing countries range from 50% to 89% [1,2].

Renal embryogenesis is the core of WT pathophysiology. During healthy nephrogenesis, the metanephric mesenchyme differentiates into epithelial mesenchyme. Then, the nephric vesicles are formed, generating most of the differentiated cells in the fully-developed kidney. However, WT might disrupt renal development, resulting in a mixture of blastemal, epithelial, and stromal cells, and causing several renal impairments[3].

WT etiology might be explained by potential interconnections between genetic mutations and alterations in the genitourinary tract during embryological development. However, literature on WT etiology is still scarce. The genes WT1, CTNNB1, WTX, TP53, and MYCN are among the genetic markers associated with WT. The worst prognoses are frequently associated with the TP53 suppressor gene and loss of heterozygosity on chromosomes 1p, 1q, and 11p15[4,5].

WT is more frequent in children with genetic syndromes, such as the Wilms tumor-aniridia syndrome, characterized by abnormal genitourinary tract function (50% of cases develop WT); Denys-Drash syndrome, a progressive renal condition (90% of cases develop WT); and Beckwith-Wiedemann syndrome, a genetic condition marked by abnormalities in organ growth leading to dysmorphisms (10% of cases develop WT)[1, 6].

Anatomical signs of WT are mostly characterized by an initial swelling in the renal cortex, starting the initial expansion. Then, the renal tissue surround the region with swelling, forming a pseudo capsule with necrotic cells that may extend into the renal pelvis, affecting vascular and lymphatic vessels and the right atrium via the renal vein. Metastases tend to occur predominantly in the lungs and lymph nodes[7].

The WT is a significant topic in global clinical practice. Since the first report in 1971, constant updates with substantial contributions from clinical trials and group studies in North America, Australia, New Zealand, Europe, and Brazil aimed to improve disease management and increase survival rates. Notable pioneers of WT study include the Renal Tumor Study Group of the International Society of Pediatric Oncology (SIOP) , the Children's Oncology Group (COG), and the National Wilms Tumor Study Group[1, 3].

Since WT onset is subtle and has various therapeutic strategies, healthcare professionals involved in pediatric care must develop a sharp and efficient clinical reasoning process. In this sense, coherent information on the topic must be disclosed to improve decision-making and clinical outcomes in children with WT. Also, the literature lacks reviews focusing on the diagnosis and treatment of WT, highlighting the need for clarifying information on associated issues and minimizing knowledge gaps. Therefore, this study aimed to analyze the diagnostic method and treatment of WT in children.

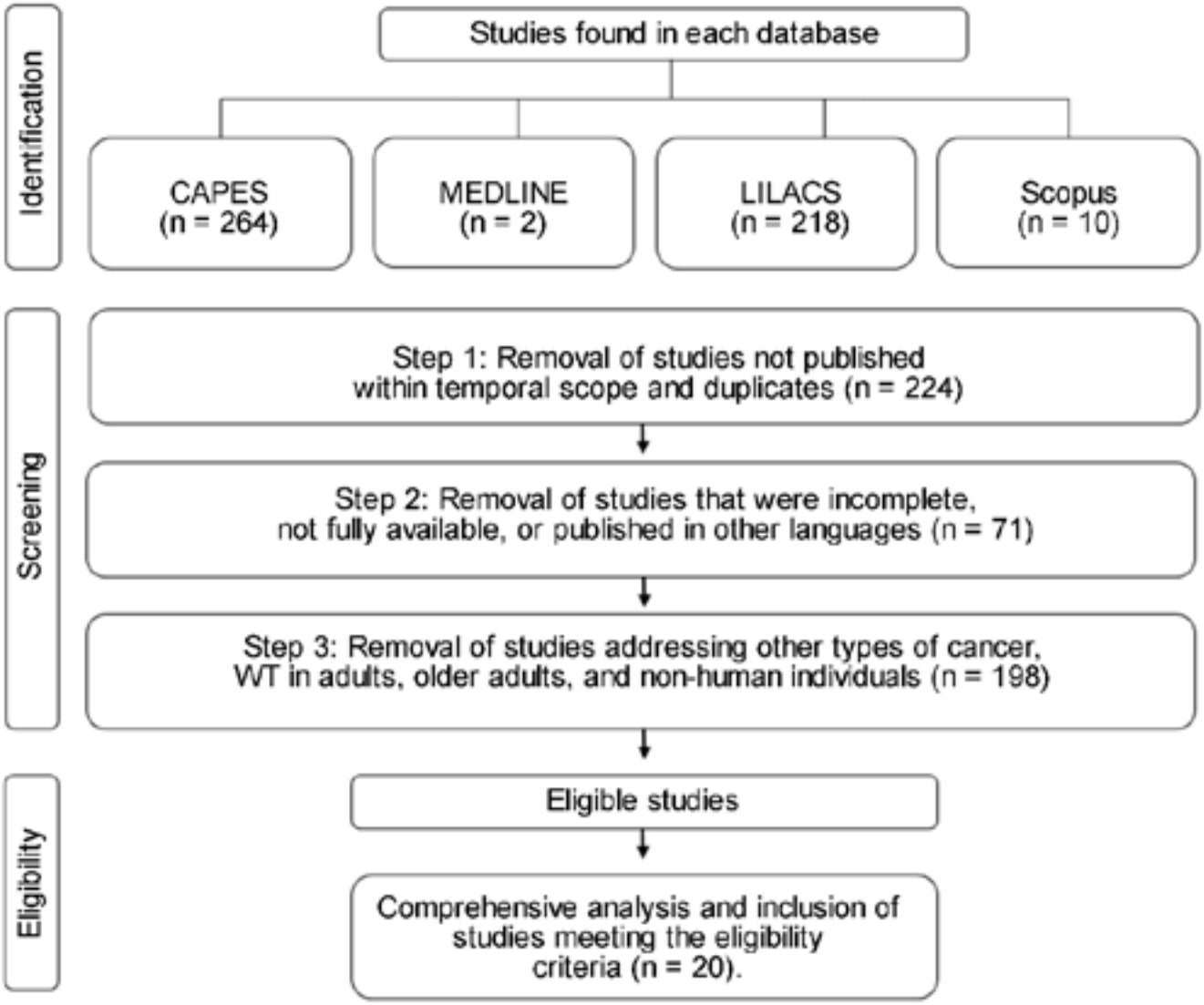
METHOD

An integrative review was conducted considering the need for consolidated information from primary studies, theoretical reviews, reports, and different types of research addressing the role of medicine in the identification and treatment of WT. This method allows a panoramic view of integral care by synthesizing knowledge from different authors [8, 9].

The search was conducted on CAPES Periodicals, Medline, Lilacs, and Scopus databases using a paired combination of the DeCS/MeSH descriptors "*Tumor de Wilms*", "*Nefroblastoma*", "*Diagnóstico*", and "*Tratamento*", between March 1 to May 20, 2022.

Inclusion criteria considered fully available scientific studies on WT in children published in the last five years and written in Portuguese, English, or Spanish. Exclusion criteria comprised studies published in other time frames, addressing divergent topics (other types of cancer, adults with WT, older adults, or studying other species), written in other languages, or not fully available. Figure 1 shows the flowchart of data screening.

Figure 1. Flowchart of data screening.



Source: Authors, 2022.

RESULTS

Table 1. Main findings of the selected studies

Title	Author	Conclusion
Bilateral Wilms tumour: a review of clinical and molecular features	Charlton J, Irtan S, Bergeron C, Pritchard-Jones K. (2017)	WT is an embryonal tumor that shows mimicry of cells of nephrogenesis. Unveiling the underlying genetic risk of bilateral WT offers a relevant challenge to maximize survival.
Dataset for the reporting of nephrectomy specimens for Wilms' tumour treated with preoperative chemotherapy: recommendations from the International Society of Paediatric Oncology Renal Tumour Study Group	Vujanić GM, D'Hooghe H, Vokuhl C, Collini P. (2021)	Due to their low occurrence, no international guideline by the International Collaboration on Cancer Reporting is currently available. COG preconizes primary surgery, while SIOP recommends preoperative chemotherapy as the initial step in management.
Histologia do Tumor de Wilms e seu impacto no prognóstico da doença	Gonçalves EVMC, Silva VLCD, Gonçalves VVMC. (2022)	WT features a unique cytoarchitectural pattern in which anaplasia adversely affects prognosis. Consequently, histopathological analysis is critically relevant.
Intra-tumor genetic heterogeneity in Wilms tumor samples	Pereira BM de S, Azevedo RM de, Neto JC de A, Menezes CF, et al. (2019)	The genetic heterogeneity of the intratumoral milieu plays a relevant role in the clinical outcomes of children. Identifying molecular markers is a current research topic by COG and SIOP groups.
Synchronous Bilateral Wilms Tumor: Surgical Evaluation and Survival	Silva JMM, Kipper ACS, Neves BH dos S, Borges DS, et al. (2021)	Protocols, such as COG and SIOP, are essential for developing WT treatment. Preservation of the renal parenchyma is advised upon the compatibility of patient variables.
Synchronous Bilateral Wilms Tumor: Surgical Evaluation and Survival	Oliveira PB, Grabols MF, Lima FFda S, Faria PAS, et al. (2018)	Conservative surgeries are recommended in bilateral WT cases managed in major referral centers.
The UMBRELLA SIOP-RTSG 2016 Wilms tumour pathology and molecular biology protocol.	Vujanić GM, Gessler M, Ooms AHAG, Collini P, et al. (2018)	The UMBRELLA protocol aimed to assess new prognostic factors. However, large international databases are needed for better follow-up of subgroups with negative prognoses.
Tumor de Wilms: análise das características clínicas e epidemiológicas	Turmina L, Voigt AD, Rodrigues AJS, Hata MM, Fiori CMCM. (2021)	WT is known to be the most common renal cancer in children (95%), resulting from a disturbed glomerular development of the kidney. Nonetheless, more reliable epidemiology data are needed.
Tumor de Wilms en riñon en herradura	Molina A, González F, Hernádez E, Bolaños J. (2021)	Few documented cases of horseshoe kidney associated with WT are available. However, nephroblastoma in this population is potentially associated with syndromic origins. Surgical intervention should prioritize the preservation of renal function.
Tumor de Wilms: Uma revisão de 15 anos de experiência recente	Illade L, Hernandez-Marques C, Cormenzana M, Lassaletta A, et al. (2018)	Studying WT is necessary, considering its epidemiological relevance. Protocols such as COG and SIOP sustain treatment practices.

Tumor de Wilms y otros tumores renales	Sánchez C, Ciordia TC (2021)	Physical examination often leads to the accidental discovery of an asymptomatic mass. In specialized services, diagnosis is given by clinical findings radiological, and histological information. The treatment typically involves chemotherapy and surgery.
Unmet needs for relapsed or refractory Wilms tumor: Mapping the molecular features, exploring organoids, and designing early phase trials – A collaborative SIOP-RTSG, COG, and ITCC session at the first SIOPE meeting	Brok J, Mavinkurve-Groothuis AMC, Drost J, Perotti D, et al (2021)	The recurrence of WT should undergo a comprehensive molecular characterization and be enrolled in protocols or trials including systematic data collection and reporting. It is crucial to improve the enrollment rates of children with WT in trials at the initial phase.
Update on Wilms Tumor. Journal of Pediatric Surgery	Aldrink JH, Heaton TE, Dasgupta R, Lautz TB, et al.(2018)	New insights into current diagnostic evaluation, surgical standards, and the impact of surgical intervention on risk stratification require further discussion.
Outcome of Nephroblastoma Treatment According to the SIOP-2001 Strategy at a Single Institution in Argentina.	Cafferata C, Cacciavillano W, Galluzzo ML, Flores P, et al. (2017)	The SIOP-01 protocol proposes a viable treatment strategy, presenting positive results for the institution.
Wilms Tumor	Haegner MJK, Villegas AZ, Calvo DM, Chavarría (2020)	The tumor, with sporadic clinical presentation, has been associated with genetic syndromes.
Wilms Tumor	Spreafico F, Fernandez CV, Brok J, Nakata K, et al. (2021)	The prognosis for children with WT is currently based on clinical, pathological, and molecular findings. In some cases, conventional cytotoxic agents, chemotherapy, surgery, and radiotherapy are considered.
Wilms tumor: 15 years of experience at a children's hospital in Córdoba	Seminara C, Planells MC, Pogonza RE, Morales M. (2019)	The most relevant prognostic factor identified was histology; however, children required long-term nephrological follow-up to confirm this hypothesis.
Wilms' Tumor – an unusual disease	Duarte ML, Duarte ER, Ferrreira JB de AF (2020)	Although clinical and imaging evaluation facilitates the diagnosis of pediatric renal tumors, histopathological examination remains indispensable.
Wilms Tumor and its recent advances	Ostrowski RV, Valentini MGT, Silva AR da, Trindade AF. (2022)	The tumor occurs mostly in children under 10 years old, resulting from abnormal proliferation of metanephric blastema cells.

WT: Wilms tumor, SIOP: International Society of Paediatric Oncology, COG: Children's Oncology Group.

DISCUSSION

Since the most frequent sign of WT is an asymptomatic abdominal mass, most children are diagnosed during routine pediatric consultations [3,4,10,11]. However, other signs may be associated with WT, such as abdominal pain and distension, gross hematuria, varicocele, hypertension or hypotension (normalized after nephrectomy), fever, anemia, and dyspnea (in cases of pulmonary metastasis).

Imaging exams (e.g., computed tomography and magnetic resonance imaging) are accurate for identifying, differentiating, and staging the tumor. Literature shows that complementary assessment is relevant for presumptive diagnosis, preoperative planning, and metastasis assessment. [2,6,12] Due to the absence of radiation and facilitated access, ultrasound is usually one of the first tests requested. Computed tomography facilitates visualizing lymph nodes and adjacent organs, further contributing to tumor staging.

Histology is often considered an essential examination to confirm the diagnosis of WT. Among the microscopic characteristics, a triphasic tumor pattern predominates, in which blastemal, mesenchymal, and epithelial cells are arranged in multiple proportions. In rare cases, tumors may be presented in a biphasic or monophasic pattern, characterized by the occurrence of anaplastic cells providing an important histological marker in risk stratification[10,13,14]. Thus, tumors are classified as low, intermediate, or high risk[1].

A new study protocol for pediatric renal tumors has been established based on evidence from the SIOP. Risk stratification is structured into five stages: stage I (limited to the renal area and complete surgical resection is facilitated), stage II (tumor expansion covers adjacent areas, but resection is still possible), stage III (tumor spread to adjacent structures and complete surgical resection impracticable; abdominal vascular or lymphatic beds are potentially affected and tumor rupture may be present), stage IV (hematogenous metastases or affecting lymph nodes outside the abdomen area), and stage V (bilateral tumor)[15]. Thus, histological stratification and tumor characterization (type, size, invasion of adjacent structures, metastases, and lymph node affected) are mandatory for the final diagnosis[16].

Before starting the treatment, differential diagnosis is essential to exclude neuroblastoma and other renal tumors (including clear cell renal sarcoma), congenital mesoblastic nephroma, renal cell carcinoma, and medullary renal carcinoma[1 6,17].

Regarding the type of therapy applied, the SIOP (widely used in Europe) and the COG (widely used in the USA) guidelines present divergencies. The COG indicates nephrectomy early in WT onset, while the SIOP initially suggests pre-surgical chemotherapy (except in children under six months of age) to prevent tumor rupture and the need for radiotherapy[12, 18]. Both guidelines present similar survival rates

In the postoperative period, indications vary according to the staging grade[19]. In stage I chemotherapy is not required in low-risk cases. However, vincristine and actinomycin for four weeks are prescribed in intermediate-risk cases. High-risk cases are treated with vincristine, actinomycin, and doxorubicin for 27 weeks[1].

In stages II and III, treatment with vincristine and actinomycin for 27 weeks is indicated for low or intermediate-risk tumors. However, for high-risk tumors, cyclophosphamide, doxorubicin, etoposide, and carboplatin are indicated. In stage IV, The combination of vincristine, irinotecan, cyclophosphamide, carboplatin, etoposide, and doxorubicin is recommended [1, 20].

Adjuvant radiotherapy is indicated in high-risk stage II, intermediate or high-risk stage III, preoperative or intra-operative tumor rupture, and cases presenting macroscopic peritoneal deposits. Pulmonary radiotherapy is also indicated for children stratified with high-risk cases and pulmonary metastases[1].

Children with bilateral WT (5% to 8% of cases[21]) are treated with preoperative chemotherapy followed by conservative surgery (resection of tumor leaving a safety margin and best preservation of the organ) and postoperative chemotherapy. Radiotherapy may also be indicated in some cases. Therefore, nephron-sparing surgery is performed to avoid intense nephrectomy. This approach might control the disease and protect the kidneys prone to relevant renal

failure[12, 22].

Children with WT may present higher risk of other chronic conditions than the general population. These conditions include secondary tumors, especially breast cancer, sarcomas, and lymphomas. The risks of renal failure, pulmonary fibrosis, ototoxicity, fertility problems, and cardiac abnormalities are also present[1, 19, 23].

The WT prognosis remains positive in most cases; however, it may vary according to histological type, disease stage at diagnosis, and adherence to the multidisciplinary treatment (psychologists, pediatricians, social workers, pediatric surgeons, anesthesiologists, radiologists, oncologists, and nursing staff)[24]. Also, the survival rate for children in stages I and II may reach 90%, while stages III and IV may reach 70%[10].

CONCLUSION

Early diagnosing WT affects its prognosis on children, highlighting the importance of physical examination in routine assessments. Clinical and complementary assessment (using imaging exams) by clinicians, immunologists, and histopathologists is essential to the diagnostic and to obtain descriptive tumor information. Available treatments include chemotherapy and conventional (or conservative) nephrectomy, which may be combined with radiotherapy.

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