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Review Article

Screening pediatric testicular cancer: A literature review

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Summary

Introduction: Childhood cancer is the leading cause of death in patients aged 5-19 years. Testicular tumors (TT) comprise 1 to 2% of all pediatric solid tumors. Although rare, TTs are often misdiagnosed. Screening improves clinical practice and decision-making for early diagnosis.

Objective: To analyze the screening methods for detection of pediatric testicular cancer and contribute to the management of suspected cases.

Methods: We conducted an integrative systematic review of the PubMed, EMBASE, and LILACS databases limited to records published between January/2013 and August/2018.

Results: Sixty articles were initially selected based on the presence of specific search terms on the article body, title, and abstract. Of those, nineteen articles were selected for a full review. Clinical signs were not evident in most studies, but 12 (63%) reported the presence of scrotal masses. Cryptorchidism, family history, and the presence of contralateral TT were identified as risk factors. Alpha-fetoprotein (AFP) was elevated in 73% of studies, but normal levels do not rule out a suspected diagnosis. Scrotal ultrasound (US) was instrumental in 73% of studies and Doppler US (32%) was able to detect nearly 100% of cases at diagnosis. Computed tomography (abdomen/chest) was required in 12 studies (63%) for confirmation of metastasis of testicular germ cell tumors. In 73% of studies, stages were subdivided based on the levels of serum tumor markers and the presence of metastasis. The inguinal-scrotal approach is suggested as the preferred method as it does not affect prognosis or require adjuvant therapy. There are minimum requirements for therapeutic retroperitoneal lymphadenectomy. In 14 studies (73%), advanced stages showed a good prognosis with surgery in combination with chemotherapy. TT histology and treatment are different for prepubertal and postpubertal patients. In the same 14 studies (73%), relapsed patients received chemotherapy. In eight studies (42%) the overall survival increased by five years and, in three of them, it increased 2 by 100% post-combination therapy.

Conclusion: Few studies have evaluated the prognosis, disease recurrence, and survival rates of children with testicular cancer. AFP, US and an appropriate surgical approach provide optimal personalized treatment and minimize the adverse effects.

Abbreviation

AFP: Alpha-Fetoprotein; GCTs: Germ Cell Tumor; Hcg: Human Chorionic Gonadotrophin; MGCT: Malignant Germ Cell Tumors; OS: Overall Survival; RPLND: Retroperitoneal Lymph Node Dissection; TT: Testicular Tumor; US: Ultrasound

Introduction

Childhood cancer accounts for 5% of all childhood malignancies. Testicular tumors are uncommon in children, comprising approximately 1% to 2% of all solid tumors. These tumors are commonly diagnosed between the ages of 4 and 18 and are typically classified by their origin as germ cell tumors and non-germ cell tumors [1,2]. Malignant germ cell tumors of the testis are rare in children, in contrast to adolescents and post-pubertal adults, of which the most common types are yolk sac tumors and teratomas (tumors with a single histologic type). Testicular germ cell tumors (GCTs) are the most

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common type of testicular tumors across all ages and comprise a heterogeneous group of cancers that share a common origin from progenitor germ cells. Testicular GCTs include yolk sac tumors, teratomas, mixed germ cell tumors, and seminomas, whereas gonadal stromal tumors include Leydig, Sertoli, granulosa cell tumors, and mixed gonadal stromal tumors. The annual incidence of testicular tumors in children is estimated to be between 1.6 and 2 per 100,000 children [3,4]. In adolescents aged 15 to 19 years, the incidence of diagnosis increases to 32.6 cases per million and represents 14% of all cancer in this population [5]. In most cases, testicular tumors present as a scrotal mass. However, the differential diagnosis of testicular cancer requires ruling out hydrocele, testicular traumas, hernia, and calcifications in cases of epididymal orchitis. The classic physical exam finding is a palpable mass (79%) with no signs of inflammation. Pain may occur with or without an increase in scrotal volume. A retrospective review of pediatric patients with testicular tumor showed that of the 61 patients analyzed, six cases were misdiagnosed as hydrocele, four cases as inguinal hernia, two cases as testicular inflammation, and one case as adenoma, all of which were misdiagnosed for presenting with a painless scrotal mass. This finding provides valuable 3 information for physicians because even though testicular cancer in children is rare, it is often misdiagnosed [6]. If a malignant tumor is suspected, specific markers such as alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) may aid in the diagnosis of germ cell tumors. In the presence of a solid scrotal tumor, complementary imaging exams such as chest teleradiography, scrotal ultrasound (US), or computed tomography of the abdomen are essential prior to a surgical procedure [7]. Of the imaging exams, scrotal US Doppler can better distinguish certain benign conditions such as hydrocele or varicocele from a potentially malignant solid tumor. Nowadays magnetic resonance is a supplementary technique to make a differentiation in inconclusive ultrasound cases and this exam could confirm pelvic node and abdominal extension [8]. Differential diagnosis of benign pathologies including, among others, epididymitis, hernia, hydrocele, and spermatic cord torsion must be established. The appropriate surgical approach is important for diagnostic confirmation and may range from a biopsy to the excision of the entire testis testicular tumors, the investigation of regional (inguinal) and distant (retroperitoneal) lymph nodes complements staging and helps determine the adjuvant therapy regimen on confirmation of cancer. Different staging systems are used for pre-pubertal and post-pubertal patients and risk groups should be used to determine treatment regimens in patients with the disseminated (metastatic) disease. The standard comprehensive treatment is surgery combined with chemotherapy, yielding a five-year overall survival (OS) rate of 75% - 100% for children with malignant germ cell tumors (MGCT) [3].

Objective

This study aimed to review the application of protocols for the evaluation and diagnosis of pediatric testicular cancer and update health professionals on the appropriate management of suspected testicular cancer.

Methods

We conducted an integrative review of the literature on pediatric testicular tumors published between January 2013 and August 2018 in three databases: PubMed, EMBASE, and LILACS. The inclusion criteria were: articles available online, indexed over the last five years, published in English, and addressing testicular tumors in pediatric patients (< 20 years old). Abstracts from Scientific meetings and case reports were excluded. The study consisted of the following phases: analysis of the publication title; analysis of the full text; article classification; full review of selected articles; articles selection; summary of key topics; data extraction and analysis. A search update was performed on July 21, 2022, to retrieve studies not covered by the initial search (2018 to 2022). (**PRISMA RESEARCH BASIS**).

Results

Firstly, 763 articles including the following key terms, according to the DeCS/Mesh database, were selected from PubMed: a) article and title: testicular neoplasms, adolescent, child, pediatrics, and humans; b) abstract and title: testicular, testis, neoplasm, tumor, tumor, carcinoma, cancer, adolescent, child, teen, pediatric, and pediatric. Next, the above terms were cross-searched on title and abstract, yielding 332 articles. The search was further refined on the title, retrieving 49 articles. The following studies were excluded: one abstract from a scientific meeting, six case reports, nine studies that the focus was not the study theme, and eight studies that could not be accessed. Eleven studies were retrieved from EMBASE using the above terms, of which eight were scientific meeting abstracts and were, therefore, excluded. One article was retrieved from LILACS, but it was not in English. One article was retrieved from both the EMBASE and LILACS but fell outside the study criteria and was therefore excluded. Of the 28 articles selected from the three databases for a full review, nine were excluded because they did not address the object of this study. Finally, 19 articles addressing screening of pediatric testicular cancer were selected for data extraction, critical and detailed analysis, and synthesis of findings. There was a consensus among most studies that, during childhood, physical examination by a pediatrician or health professional is a reasonable surveillance strategy for testicular and scrotal symptoms. In adolescence, self-examination will aid in the detection and prevention of testicular tumors. Clinical signs are usually not evident and may be associated with scrotal pain or swelling, scrotal mass, history of undescended testis, inguinal hernia evaluation, history of varicocelectomy, trauma findings, or testicular asymmetry. Göbel, et al. (2014) reported the presence of inguinal pain, back pain, or dysuria in some cases [9,10]. Risk factors for pediatric testicular cancer are well established and include cryptorchidism, history of contralateral testicular tumor, family history, and infertility or subfertility. In addition, Chien, et al. (2014) reported that height is another established risk factor for testicular germ cell tumors [11,12] In that study, most tumors were diagnosed at 0 – 19 years, but there were differences in incidence and clinical presentation among group studies [13]. Similarly, Karmazyn, et al. (2018) compared the

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malignancy risk of primary testicular tumors in children in the pre-pubertal period (5–12 years) with younger (0–4 years) and postpubertal (13–18 years) children [2]. In patients aged 13–18 years, the most common malignant tumors were germ cell tumors (44%, 11/25), eight (72.7%) of which were mixed germ cell tumors and three of these cases progressed with metastasis. At 0-4 years, 63.6% were diagnosed with juvenile granulosa cell tumors. Preadolescent children between ages 5 and 12 years with testicular masses had benign conditions mimicking a tumor on ultrasound and unique characteristics that were significantly different compared with the other age groups. No child had elevated tumor markers (AFP or hCG). Similar results were reported by Amini, et al. (2016), who examined a sample of 1,496 adolescents (13-19 years) diagnosed with testicular germ cell tumors. In this age group, approximately 90% of testicular germ cell tumors are non-seminomas. Adolescent patients were more likely to present with more advanced disease at diagnosis than adults independent of pathologic diagnosis [14,15]. Serum AFP levels are elevated in most pediatric cases (90%), but the absence of elevated levels does not rule out a suspected diagnosis. Human chorionic gonadotrophin (hCG) and lactate dehydrogenase (LDH) are also useful in monitoring testicular tumors. Staging is based on the presence and levels of serum tumor markers and on the determination of the anatomic extent of disease [4,7]. According to Epifanio (2014), testicular teratoma has a very variable appearance and can simulate that of other lesions [16]. The testicle can have an increased or a normal volume. The scrotal US is instrumental in the diagnosis and has the added advantage of detecting tumors that are nonpalpable on physical examination, aiding in early detection. Doppler US can detect testicular neoplasms in nearly 100% of reported cases [17,18]. Patients with microlitiasys in ultrasound testicular exams have been reconsidered to differential diagnosis in testicular câncer [19]. According to Grantham, et al. (2016), computed tomography (CT), the magnetic resonance of the abdomen/pelvis, or additional imaging such as chest x-rays, should be used for the staging of testicular cancers, especially germ cell tumors with suspected metastasis [20]. Because tumor histology differs between pre-pubertal and post-pubertal patients, treatment options may also differ. Radical inguinal orchiectomy with high ligation of the spermatic cord is the standard of care in the initial treatment of testicular cancer. The inguinal 6 approach is preferred over scrotal manipulations, which affects staging and avoids the potential spread of disease. After the tumor type has been determined by the histopathologist, the physician will recommend the treatment plan and options, which include routine monitoring, adjuvant chemotherapy, lymphadenectomy, and radiotherapy. Retroperitoneal lymph node dissection (RPLND) guidelines vary depending on the origin of the tumor; for instance, the procedure is not recommended in pre-pubertal patients with yolk sac tumors. Conversely, this approach is of therapeutic importance in adolescents with mixed cell tumors. According to Chung (2014), there are minimum requirements for therapeutic RPLND. Relapsed patients can be treated with chemotherapy. Advanced stages also show a good prognosis with surgery and chemotherapy. The correct first approach is essential after testicular cancer tumor, surgery, correct staging, and chemotherapy, in Italian protocol studies germ-cell tumors have an overall survival and goog relapse-free survival [21]. Metastasis typically occurs by both lymphatic and hematogenous spread [1-22]. Protocols for children with testicular cancer recommend surveillance of all stage I cases and careful evaluation when prescribing chemotherapy in metastatic disease cases. Cornejo, et al. (2014) reported that most patients showed no signs of disease after orchiectomy and minimal adjuvant therapy. Cost, et al. (2014) reported that survival increased from 38% to 100% in stage I cases. Cornejo, et al. (2014) and Göbel, et al. (2014) estimated an increase in five-year overall survival in patients with testicular cancer independent of patient age [7-12]. However, there are data available on disease-free survival or overall survival rates for testicular cancer in adolescents. Survival for Pediatric testicular tumors depends on the presentation, the clinical suspicious, and after treatment the correct Outcome [23,24].

Conclusion

Testicular tumors are rare in children and account for only 1% of all pediatric solid tumors and 3% of all testicular tumors. Few studies have evaluated the prognosis, disease recurrence, and survival rates of children with testicular cancer. AFP and US are important in monitoring tumors. Appropriate surgical procedures provide optimal personalized treatment and minimize adverse effects. Screening enables the synthesis and interpretation of the current knowledge on testicular tumors in children and adolescents, contributing to improving clinical practice and decision-making. This review highlights the importance of early diagnosis of testicular cancer by carefully performing physical and imaging exams.

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