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Testicular Cancer: The Most Common Malignancy in Young Men – A Review of Current Knowledge on Diagnosis and Treatment

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ABSTRACT

Background. Testicular cancer is a rare malignancy that primarily affects young men and requires early diagnosis. The diagnosis is based on clinical tests, imaging tests and measurement of tumor markers. Treatment consists mainly of surgery, and further therapeutic management is adapted to the tumor type and stage.

Aim. The aim of this study was to review the literature on testicular cancer, including risk factors, prevention, diagnosis, and treatment.

Method and Materials. The literature review was conducted based on publications retrieved from the PubMed, Google Scholar, and Web of Science databases, using the keywords: testicular cancer, epidemiology, diagnostics, cancer markers, and treatment.

Results. Regular monitoring of risk factors, testicular self-examination and attention to symptoms increase the likelihood of early detection of testicular cancer by patients. Prompt initiation of appropriate therapy allows effective disease control and improves survival outcomes

Conclusion. Testicular cancer requires special diagnostic vigilance, and early therapeutic intervention is crucial for effective treatment.

Keywords: testicular cancer, epidemiology, diagnostics, cancer markers, treatment

Introduction

Testicular cancer is a rare malignant tumor that develops in the male sex glands located in the scrotum. This condition mainly affects young men, most often between 15 and 35 years of age, and more than 90% of cases originate from germ cells. Despite its low incidence in the general population, it is one of the most frequently diagnosed cancers in this age group, which resulting in a significant number of new cases and deaths registered each year [1,2,3]. A recent analysis of data from the GLOBOCAN database showed that in 2020 the global age-standardized incidence rate (ASR) was 1.8 per 100,000 person-years, with clear differences in the incidence of the disease between different regions of the world [4]. The diagnosis is based on clinical and radiological assessment, as well as measurement of tumor marker concentrations. The treatment of choice is orchidectomy, and in selected cases, chemotherapy is used after the procedure to reduce the risk of recurrence of the disease [5].

Description of the state of knowledge

1. Classification

Testicular cancer is divided into two main histological groups: germ cell tumors (GCT) and non-germ cell tumors (NSGCT). GCTs develop from primary germ cells, and their precursor lesion is neoplasia in situ. On the other hand, NSGCTs, which include embryonal carcinoma, choriocarcinoma, yolk sac tumor and teratoma, often show a mixed histological composition, with teratomas rarely transforming into a secondary somatic tumor with similar biology.

Germ cell tumours account for the vast majority of testicular cancer cases, covering 90-95% of all diagnoses, and are histologically divided into seminomas, non-seminomas, spermatocytic spermatomas, and mixed forms. Seminomas constitute approximately 55–60% of GCTs, while non-seminomas make up 40–45%. Spermatocytic seminomas are very rare, usually indolent and account for only about 0.6% of all germ cell tumors [6,7,8].

2. Epidemiology

Testicular cancer is one of the most common malignancies in young people, especially in the age group of about 15-35 years, with the highest number of cases usually recorded between

20 and 34 years of age. Although this disease can appear at any age, its occurrence is concentrated primarily in the population of young adults. Overall, this cancer accounts for about 1% of all cancers in adults and about 5% of genitourinary cancers. In Western countries, the incidence of the disease is on average between 3 and 11 new cases per 100,000 men per year. It is estimated that in 2020, about 74,000 new cases of this disease were diagnosed worldwide, while in the United States, nearly 9,800 new cases were forecast in 2024.

The prevalence of testicular cancer varies by region and ethnicity, with the highest rates in Europe and North America, while much lower rates are observed in Asia and Africa. In the U.S, incidence is the highest among non-Hispanic white men and the lowest among black, Asian and Pacific Islander residents. There is an increasing number of diagnosed cases among Hispanic men, which highlights the importance of increasing awareness of the disease, early diagnosis, and prompt implementation of treatment [8,9,10].

Projections indicate that by 2035, the incidence of this cancer in Europe may increase by about 21%, suggesting an increasing risk of developing the disease regardless of the aging of the population. At the same time, a downward trend is observed in some countries with a high prevalence of the disease, such as Denmark or Switzerland. A different trend is expected in parts of Southern Europe, for example, in Spain, where the number of new cases is forecast to decrease by about 12% [11].

3. Risk factors and symptoms

The key risk factors for the development of this disease include, among others, cryptorchidism, the occurrence of testicular cancer in the family, gonadal dysgenesis, fertility problems or genetic predisposition, including Klinefelter syndrome [12].

Cryptorchidism, failure of the testicle to descend properly into the scrotum, is one of the most important factors predisposing to testicular cancer. In these men, the risk of developing it is 4-8 times higher than in the general population. The position of the testicle and the timing of the surgery are important – the higher the testicles and the later the surgical intervention, the greater the likelihood of developing a malignant tumor [13].

The presence of testicular cancer in the family is another important risk factor, especially in first-degree relatives. The risk of developing the disease is also higher in families with a history of other cancers, including melanoma, mesothelioma or neuroepithelial tumors, which may indicate hereditary cancer syndromes. In addition, people with a family history of this cancer are more likely to have cryptorchidism, a younger age of diagnosis, and may be exposed

to common environmental factors in childhood [14].

Male infertility is an important risk factor for developing testicular cancer. Studies indicate that men with fertility disorders, especially those with abnormal sperm parameters, are up to 3-20 times more likely to develop this cancer compared to the general population. Despite the proven link, the exact mechanisms of this relationship have not been fully understood, so it is important that patients with infertility remain under regular medical monitoring and are assessed at risk of developing this cancer [13,15,16].

In patients diagnosed with this disease, the presence of reproductive cell tumor in situ is often observed, which is considered to be a lesion that precedes the development of the tumor. It is estimated that it occurs in about 8.6% of patients and its presence is associated with increased risk of tumor in the contralateral testis [17].

The most common symptom of testicular cancer is a painless, well-felt mass in the scrotum, often accompanied by discreet asymmetry or a feeling of heaviness. Some patients experience testicular swelling or hydrocele, and less commonly, patients may experience acute pain due to rapid tumor growth or intratumoral hemorrhage. In some cases, the lesion may be detected accidentally during an ultrasound examination. In advanced stages of the disease, general symptoms such as weight loss, weakness or lack of appetite are observed, as well as symptoms associated with metastases, such as back or abdominal pain, enlargement of the supraclavicular lymph nodes, haemoptysis or gynecomastia [13,18,19].

4. Diagnostics

4.1 Self-examination

Early diagnosis of testicular cancer largely depends on the patient's awareness of the first symptoms of the disease and regular testicular check-ups. If an abnormality is detected, a medical consultation is necessary, and the diagnostic test used when a change in the scrotum is suspected is ultrasonography, which allows for the assessment of its location, size and nature. One of the key non-invasive methods for early detection of this cancer is testicular palpation, which can be performed by the patient, a healthcare provider, or a partner. Self-examination consists of carefully observing the scrotum and then carefully examining each testicle using both hands, which allows you to detect possible abnormalities. It is recommended to carry them out once a month, especially for men aged 15-45, preferably during a bath or

shower. However, despite its simplicity and non-invasive nature, this method is still not widely used in many countries in Europe and North America. As in the case of many other cancers, the prognosis in this disease largely depends on the moment of its diagnosis, so early detection is crucial for the effectiveness of treatment [20,21,22].

4.2 Ultrasound

Scrotal ultrasound is the main imaging method used in the diagnosis of testicular cancer and is an important complement to physical examination. This examination allows for a thorough assessment of the structure of the testicles and the detection of the presence of possible focal changes. With a properly performed examination, it is possible to diagnose even very small changes within the testicle. On ultrasound, seminomas usually reveal themselves as relatively homogeneous masses with reduced echogenicity. However, they may contain small structures resembling septa, small cysts or microcalcifications.

Non-seminomatous tumors, on the other hand, are characterized by more varied echogenicity and irregular boundaries, which result from the presence of hyperechoic foci, necrotic lesions, scarring, calcification or haemorrhage. In this type of cancer, larger cysts are often observed, especially in mature teratoma.

Ultrasonography remains the basic method in the diagnosis of this cancer however, a full evaluation of both testicles and accurate diagnosis require supplementation with other additional imaging techniques [13,23].

4.3 Tumor markers

Cancer markers such as alpha-fetoprotein (AFP), lactate dehydrogenase (LDH) and beta-hCG are a key component of testicular tumour diagnosis. In the AJCC TNM classification for testicular cancer, elevated concentrations of these markers form a separate category "S", which is specific to this cancer, which allows for the assessment of the stage of the disease and prognosis. They should be determined both before and after orchidectomy to support accurate diagnosis and monitoring of treatment. In the case of pure seminoma, the correct concentration of AFP is required, and its elevation suggests the presence

of a non-seminomatous germ cell tumor, whereby mild, stable deviations may not indicate a histological change. Beta-hCG and LDH levels may also be elevated, however they are not sufficient

alone to stage disease or assess risk and must be interpreted carefully [24,25].

4.4 Magnetic resonance imaging (MRI)

MRI is not a standard test in the initial identification of testicular tumors, but it can complement the diagnosis, especially when the ultrasound results are ambiguous or the precise location of the lesion in the scrotum is difficult [26,27].

4.5 MicroRNA

MicroRNAs (miRNAs) are emerging as promising new biomarkers in the diagnosis of testicular cancer. These are small RNA molecules involved in the epigenetic regulation of gene expression and influence numerous cellular processes. Their elevated levels in testicular tumor tissue are associated with the regulation of genes involved in germ cell differentiation and with mechanisms related to fertility disorders. For this reason, miRNAs are of interest as potential tools to support the diagnosis and monitoring of germ cell tumors. Studies indicate that selected microRNAs, especially miR-371a-3p, may demonstrate higher diagnostic accuracy than classical tumor markers. This marker shows high sensitivity and specificity in detecting the disease, and its level may also reflect the response to treatment at different stages of cancer. miRNAs are also considered potentially useful for the early detection of disease recurrence. Clinical trials focus on evaluating the practical utility of miRNAs in controlling the course of testicular germ cell tumors. However, standardization of laboratory procedures for miRNA analysis and assessment of the costs and potential impact on the healthcare system remain significant challenges. Nevertheless, this research is necessary to fully determine the role of miRNAs in the diagnosis, monitoring of treatment and care of testicular cancer patients [28,29,30,31].

5. Treatment

The primary procedure for most patients with suspected testicular tumours is orchidectomy, which involves the removal of the testicle along with the spermatic cord.

Testicular-sparing surgery is rarely recommended, but may be considered for small unilateral or bilateral tumors. In the case of patients diagnosed with pure seminoma, further management after the procedure may include observation or additional treatment methods, such as chemotherapy, radiotherapy or surgical interventions, depending on the stage of the disease. Therapeutic decisions are based on the results of the histopathological examination, the assessment of the risk of recurrence and the patient's preferences. The modern approach focuses on minimizing the side effects of treatment by selecting therapies tailored to the level of risk. Although risk-based strategies are more widely used in non-seminomas, in the case of seminomas they still require careful assessment and individualization of management [24,32].

Patients with stage I seminoma after orchidectomy are closely monitored, including follow-up visits and abdominal imaging. If necessary, cancer markers are also evaluated. The greatest risk of recurrence falls on the first three years, so check-ups are more frequent during this time. Usually, recurrence is detected thanks to imaging tests, and marker or chest tests are performed mainly when cancer recurrence is suspected. Such a regimen allows for rapid implementation of treatment and ensures almost complete disease-dependent survival [33].

Radiotherapy or platinum-based chemotherapy is used to treat stage IIA and IIB seminomas, and primary retroperitoneal lymph node resection (RPLND) is an effective alternative with low long-term morbidity. In patients with advanced stage disease (IIC/III), risk-adjusted induction chemotherapy is the treatment of choice, while primary surgery is of minimal importance. After the completion of first-line chemotherapy, patients should undergo imaging tests such as CT or MRI of the chest, abdomen and pelvis, as well as determination of tumor markers in the blood. Individuals whose AFP and beta-hCG levels are normal and whose residual mass is absent or does not exceed 3 cm may only be included in observation [24,34].

On the other hand, stage I non-seminal germ cell tumours are most often followed, although in some cases patients are given one cycle of BEP chemotherapy, i.e. bleomycin, etoposide and cisplatin, or adjuvant RPLND. In stage II, treatment depends on the stage – patients may receive primary RPLND or chemotherapy, with primary retroperitoneal lymph node removal (pRPLND) being preferred in those at low risk of recurrence and chemotherapy in patients at higher risk. On the other hand, in stages IIC and III, the standard is chemotherapy adapted to the risk group according to the International Group of Cooperation on Germ Cell Cancer (IGCCCG), after which they are surgically removed in the presence of larger residual masses [13].

Resistant germ cell tumours are rare and highly diverse, and traditional therapies targeting specific mutations or signalling pathways have not yet yielded significant efficacy. A new approach is CAR-T therapies, in which the patient's T cells are modified to recognize the surface antigen claudin-6, which is present in most germ cell tumors. Preliminary results of phase I/II studies show promising effects of this therapy in the treatment of resistant cancers [35].

Currently used chemotherapy regimens allow most patients to be cured of germ cell tumors. As the disease mainly affects young men, it is important to also consider the long-term effects of treatment, such as cardiovascular complications, hearing disorders, neuropathy or fertility problems. Therefore, long-term follow-up of patients and the selection of such therapy that will ensure cure with the lowest possible risk of late complications are important [33].

Conclusion

Testicular cancer is a significant health problem among young men around the world, even though it is relatively rare compared to other cancers. Early diagnosis of the disease and the implementation of appropriate therapy are crucial for improving treatment outcomes. The choice of treatment method depends on the histological type of the tumor and the stage of the disease, and modern therapeutic strategies allow to achieving good results. The development of new markers, such as microRNAs, that can support the diagnosis and monitoring of the disease, has been receiving increasing attention, although their use in clinical practice requires further research. It is also important to consider the possible long-term consequences of therapy, especially in young patients. Further research into new diagnostic and therapeutic methods could contribute to even effective treatment of this cancer.

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