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Diagnostic and therapeutic management in patients suffering from prostate cancer – a review of the most important issues

Postępowanie diagnostyczno-terapeutyczne u pacjentów chorujących na raka prostaty – przegląd najważniejszych zagadnień

Jakub Husejko, Hanna Bednarek, Monika Ciekalska, Kornelia Kędziora-Kornatowska

Department of Geriatrics, Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń

Abstract

Prostate cancer is a clinically significant problem in many European countries. In Poland, prostate cancer is the second, after lung cancer, most common type of cancer. It is also the third leading cause of cancer death amid men. Age is the main risk factor. Despite its wide spread, we still face many diagnostic problems on the way to the effective detection and treatment of prostate cancer. is The fact that characteristic symptoms, allowing a clear diagnosis of this type of cancer, are observed only in the late stage of the disease is one of the major diagnostic problems for prostate cancer. In this review, we focus on epidemiology, diagnosis and its problems, we describe the available treatment strategies, and also we present the role of screening in early detection of prostate cancer. (Gerontol Pol 2020; 28; 228-233)

Keywords: *prostate cancer, PSA, androgen-deprivation therapy*

Streszczenie

Rak prostaty stanowi poważny problem kliniczny w wielu krajach europejskich. W Polsce jest drugim po raku płuca najczęstszym typem raka. Stanowi również trzecią najczęstszą przyczynę śmierci z powodu raka wśród mężczyzn. Głównym czynnikiem ryzyka rozwinięcia się choroby jest wiek. Mimo szerokiego rozpowszechnienia, na drodze do skutecznego wykrywania i leczenia raka prostaty wciąż napotykamy wiele problemów diagnostycznych. Jednym z najważniejszych jest fakt, że charakterystyczne objawy, pozwalające na jednoznaczne rozpoznanie tego typu raka, występują dopiero w późnym stadium choroby. W tym artykule poglądowym skupiamy się na epidemiologii, diagnostyce i problemach, jakie w niej napotykamy, opisujemy dostępne metody lecznicze, a także przedstawiamy rolę badań przesiewowych we wczesnym wykrywaniu raka prostaty. (Gerontol Pol 2020; 28; 228-233)

Słowa kluczowe: *rak prostaty, PSA, terapia pozbawienia androgenów*

Introduction

Cancers are diseases mainly in older people. In an aging society, we should be prepared for an increase of cancer incidence. In Poland, prostate cancer is the second, after lung cancer, most common cancer, also it is the third leading cause of cancer death amongst men [1]. Numbers of detected cancers differ throughout Europe, although the incidence of clinically diagnosed prostate cancer is highest in Northern and Western Europe [2]. The reasons can be in exogenous factors such as diet, sexual behaviour, chronic inflammation and low exposure to ultraviolet radiation [3]. Most cases of prostate cancer occur in the seventh and eighth decade of life, after the age of 60 there are 87% of cases and after the age of 70 there are 50% of cases of prostate cancer. The risk of disease increased rapidly from the sixth decade reaching the maximum after 75 years of age . On the other hand, Polish statistics are not so bad against the background of Europe, because in Poland there is 45% less morbidity than in other European countries [1].

Prostate cancer is in some way a unique type of cancer, because the incidence of histologically confirmed invasive cancer at autopsy significantly exceeds the pre-

Correspondence address: ✉ Jakub Husejko; Department of Geriatrics, Ludwik Rydygier Collegium Medicum in Bydgoszcz, 9 Skłodowskiej-Curie St.; 85-094 Bygdoszcz ☎ (+48) 725 465 576 💻 kubahusejko@gmail.com

valence of clinically significant carcinoma during life [4]. The main risk factor is age, prostate cancer is very rare in people before 50 years of age .

In most cases this tumor is asymptomatic, but it can be recognised by an increased level of prostate-specific antigen (PSA) in serum, biopsy of prostate gland and per rectum examination. Despite well-developed diagnostics, it is still impossible to define the statement about the individual patient's prognosis, which can lead to unnecessary treatment, and finally harm the patient [5]. There are some other ways to recognise this cancer, which will be presented in the next chapters of this article. Regarding therapy, there are two main ways: surgical- and radiotherapy or close clinical monitoring [1]. This report describes recent trends in epidemiology, recognition and treatment of prostate cancer.

Materials and Methods

The authors reviewed available research over the past 30 years (1990-2020) using leading electronic databases and search engines, such as Medline, ResearchGate, and Google Scholar. Keywords were used such as prostate cancer, PSA or androgen-deprivation therapy. From the available materials, articles were chosen describing most important issues regarding the diagnosis and treatment of patients suffering from prostate cancer, which should be known by all medical professionals

Results

Risk factors of prostate cancer

Besides factors known for many years, such as age or genetic predisposition, new factors still appear in the work of researchers. An example of this is the study conducted on the Finnish community. The researchers checked a correlation between antihypertensive drugs and prostate cancer risk in a Finnish population. They prove that using antihypertensive drugs was associated with increased prostate cancer risk**.** They also said that comparable risk association for multiple drug groups insinuate that the findings may not reflect a direct medication effect, but may be due to underlying hypertension [6].

In the latest reports, you can also see a lot of information about the relationship between prostate cancer and acne in adolescence. However, several researchers have carried out a meta-analysis of these studies and, as it turned out that in summary, this meta-analysis did not find an association between acne in adolescence and prostate cancer risk [7].

In 2013 research was published on obesity and its association with prostate cancer. US researchers in their work discussed the effect of obesity on the risk of cancer malignancy. In their conclusions, we can see that obesity may increase the aggressiveness of prostate cancer. Of course, the subject of these studies is still only an introduction and can be a direction for further analysis [8].

What is the BRCA1 gene associated with? When we talk about BRCA1, it is most often associated with breast cancer. As it turns out, mutations within this gene can also affect other cancers – including prostate cancer. The study which was published in 2012 shows evidence for an increased risk of PrCa in men with mutations in *BRCA1*. Scientists identified 4 deleterious mutations and 45 unclassified variants. Harmful BRCA1 mutations prove a relative risk of PrCa of ~3.75-fold, translating to a 8.6% cumulative risk by age 65 [9].

In 2014, Nature published research on the role of vitamin D in reducing cancer risk and progression. In this publication we can read about some clinical studies which suggest that vitamin D deficiency increases the risk of developing cancer and that avoiding deficiency and adding vitamin D supplements might be an economical and safe way to reduce cancer incidence and improve cancer prognosis and outcome. American scientists believe that the result is the possibility of using vitamin D supplementation in people with deficiency. It can contribute to the reduction of cancer incidents and improve cancer prognosis and outcome. [10]

Other very interesting studies concerned an increased risk of high–grade prostate cancer among infertile men. Infertile men were found to have an increased risk of later developing high–grade prostate cancer. This could be treated like an early and identifiable risk factor for the development of prostate cancer [11].

Diagnostics in physical examination

Examination of people at higher risk of prostate cancer is extremely important. It is reported that the percentage of mortality decreases drastically in people who have had no progression of neoplastic tissue towards the organs surrounding the prostate [12].

Characteristic symptoms, allowing a clear diagnosis of this type of cancer, are observed only in the late stage of the disease. The vast majority of prostate tumors (70-80%) develop peripherally in the form of small nodules and lumps that are significantly different from the soft and elastic normal prostate. Therefore, one of the diagnostic tests is DRE (digital rectal examination). The great advantage of this study is the fact that it is quick, painless, does not require any financial resources, and

its implementation is possible under the conditions of a doctor's office. In addition, other structures such as the colon rectum or urinary bladder can be assessed during this study, which further increases its value as a physical examination. On the other hand, the inability to detect the early stage of the disease is a definite disadvantage, and therefore other methods of imaging diagnostics, such as magnetic resonance imaging or TRUS (transrectal ultrasound) should be used. The data do not report the DRE study as a high diagnostic value in the case of STA, but in combination with the PSA level assessment, this study becomes a reliable determinant of disease progression. More accurate studies in high-risk groups are particularly recommendable (especially in the 65-75 age group)[13-15].

The TRUS study, i.e. the transrectal ultrasound examination, is not a routine examination, but it is used for suspected neoplastic lesions after rectal examination. Using TRUS, we can observe neoplastic changes in the prostate gland, which can not be found during the DRE examination, as well as to determine the degree of changes and their location. When prostate cancer is suspected, this study is accompanied by a biopsy for histopathological examination [17]. This test should be performed in men at increased risk (ie, family history of cancer, prostate pains). Unfortunately, as in the case of the DRE study, early stages of cancer can not be detected as a result of this study. As with any uro-genital area examination, y the psychological resistance that accompanies the patient is one of the main drawbacks of the stud [17,18].

MRI may be another available diagnostic test for prostate cancer . Initially, they were used only to assess the stage of prostate cancer, while after the introduction of modern methods of contrasting the image MRI also gained recognition in the early detection of cancer, and evaluation of its exact location. The use of PSMA specific prostate membrane antigen is one of the methods of imaging enhancement , which is overexpressed in cancer cells of the cancer by nearly 100%, in relation to normal prostate cells [16,18].

Laboratory diagnostics

Laboratory diagnostics of prostate cancer is based on the determination of a tumor marker PSA (prostate-specific antigen) [21]. Scientists are still looking for more and more reliable methods in the diagnosis and diagnosis of cancer. The ideal diagnostic marker should be 100% sensitive and specific. Unfortunately, perfect markers do not exist, although PSA is organ-specific. Detection of the appropriate concentration of PSA in the serum leads us to further diagnostics [21]. They have multiple applications in confirming diagnosis, assessing the severity of the disease process, diagnosing metastases, assessing effective treatment, monitoring treatment, and monitoring adjuvant therapy.

Serum PSA concentration may depend on its expression in the cell, the severity of cell release and the vascularity (presence of blood vessels and lymphatic vessels around the tumor) [23]. There is a correlation between the tumor marker concentration and the severity of neoplastic lesions or the mass of the tumor. Thus, the larger the tumor, the greater the concentration of the tumor marker. A patient coming to the diagnostic laboratory should be before invasive or diagnostic procedures on the prostate or 2-3 weeks after they have been performed [23]. PSA levels also increase in adenomas, after surgical procedures, prostate biopsies or per rectum tests [24]. The concentration of PSA also increases with the age of the male.

The PSA panel contains tPSA (total prostate-specific antigen), fPSA (free prostate-specific antigen) and the fPSA / tPSA index. fPSA / tPSA <10% has the highest diagnostic value , whichsuggests an increase in the probability of prostate cancer; whereas fPSA / tPSA> 25% may suggest either adenoma or normal condition [21]. In men aged 70-79, the norm is up to 6.5 ng / ml [22]. Precisely described recommendations regarding the use of tumor markers in patients with prostate cancer were presented by: NACB (American National Academy of Clinical Biochemistry) and EGTM (European Group on Tumor Markers). The decrease in serum PSA may be due to radical prostatectomy, radiotherapy, hormonotherapy (treatment with LH-RH analogues), bilateral orchidectomy and treatment with 5-□-reductase inhibitors [24].

In the diagnosis of prostate cancer, specific genes can also be identified. Increased occurrence of prostate--specific membrane antigen (PMSA) has been found in people with poor prognosis and with malignant forms of this cancer [19]. Overexpression NKX3.1, Prostate Tumor Induction Gene-1 (PTI-1), PCGEM-1, PDEF, TMPRSS2, Prostase and the gene have also been overexpressed in men diagnosed with prostate cancer [20]. The increase in gene expression is the most widely known and described genetic change in the detection of prostate cancer . This gene is on the 9q21.2 chromosome. NSE (neuron specific enolase), PAP (prostatic acid phosphatase) and hK2 (prostate-specific human kallikrein) are also supportive and complementary markers . They are not organ-specific but their increased concentration has been observed in men diagnosed with prostate cancer.

Treatment

Many ways to treat prostate cancer have developed over the years. The choice of treatment method depends on many factors: severity of the disease, risk assessment (based on PSA and Gleason score), age of the patient and expected survival. It is important to assess whether the patient needs treatment at all. Elderly patients with additional diseases often require only active surveillance. Healthy elders can be treated like younger patients [25].

Studies have shown more effective reduction of incidences of cancer progression and metastases when surgery and radiotherapy were used rather than active monitoring [26].

Localized prostate cancer is usually treated 8 to 9 weeks with radiotherapy. Trials showed that hypofractional RT is also efficient and more convenient to patients especially for those with intermediate-risk prostate cancer [27].

Radiation and surgery used as combined treatment is connected with a significant risk of urinary adverse events. One of them is urethral stricture. Those treatments carry significant long-term effects because the risk increases with time. The doctor should keep this in mind while thinking of the best option for the patient [28].

Androgen-deprivation therapy has been a very well known and commonly used treatment in prostate cancer for years. It has been proven that the combination of standard ADT and docetaxel gives longer overall survival than ADT alone in men with hormone-sensitive metastatic prostate cancer [29].

It is challenging to make an optimal decision regarding treatment of prostate cancer. The best approach is to provide patients with full information about the benefits and harms of each option, including patterns of decline in bowel, urinary and sexual function and then decide according to patients needs and associated quality of life [30].

Screening for prostate cancer

The main aim of screening is to identify the disease at the stage where it is possible to prevent patient's death and suffering. Ideally, screening for prostate cancer should provide data on cases likely to progress to life-threatening stage of the disease.This helps to avoid the overtreatment and overdiagnosis phenomena that burden the healthcare system. PSA determination and digital rectal examination - DRE are the most commonly used screening methods for prostate cancer [31,32].

In recent decades, there have been many randomized controlled trials

concerning the validity of screening in prostate cancer. In 2012, a Lumen meta-analysis was presented, which included 8 randomized clinical trials involving 571,594 men. The review was based on data collected in Medline and Web of Science databases. The main screening tools that have been used in these studies were the determination of the PSA and digital rectal examination.This meta-analysis showed a correlation between the performance of screening tests and a 24% reduction in prostate cancer mortality. However, the meta-analysis did not indicate an ideal screening strategy [32,33].

In 2010, at the 7th meeting of ESOU (EAU Section of Oncological Urology) in Vienna, the results of the ERSPC (European Screening Study for Prostate Cancer) were presented and compared with the PLCO- (Prostate, Lung, Colon and Ovary screening study) which was conducted in the USA in 1992-2001. In both studies it was tested whether screening of prostate cancer reduces the mortality rate that is specific for this cancer. They mainly used PSA measurement and digital rectal examinations in these studies. The ERSPC study showed a significant reduction in the risk of death (at least 20%) due to prostate cancer in men tested. However, the PLCO study did not show a reduction in mortality from prostate cancer screening.

Reassessment of the PLCO study revealed significant errors during the test run.

In 2017 - CISNET (Cancer Intervention and Surveillance Modeling Network) referred to the ERPSC and PLCO research and adjusted previous information about PLCO studies results. CISNET proved that both studies demonstrated a reduction in prostate cancer mortality (25-31% in ERPSC and 27-32% in PLCO) during PSA screening [34,35].

According to the Guidelines of the American Urological Association (Early Detection of Prostate Cancer) from 2013, screening is not recommended in men under age 40 years. Also, it is not recommended in men between ages 40 to 54 years, with a moderate risk of developing the disease. (in men at this age at higher risk all decisions should be individualized). According to the guidelines, screening for prostate cancer brings the best benefits in the 55-69 age group and it is not recommended routine PSA screening in men aged 70+ years or any man with less than a 10 to 15 year life expectancy. AUA also recommend 2 years interval between routine screening to reduce the harms of testing and to provide lower risk of overtreatment and overdiagnosis [36].

Conclusions

The high mortality rate in prostate cancer is due to the considerable difficulty in detecting it at an early stage of the disease due to the absence of bothersome symptoms. However, just as early diagnosis and appropriate treatment can contribute to reducing the risk of death from prostate cancer. Continuous research into the effectiveness of the therapy and methods of early detection of prostate cancer give more and more hope for healing and increasing survival among patients. Despite major advances in medicine, mortality from prostate cancer is still too high. Factors such as age and genetic burden can cause cancer cells to multiply, leading to prostate cancer. It has been proven in numerous studies that there are many more factors leading to the development of the disease. An extremely important preventive measure is making the society aware of the course of the disease and its symptoms, informing about who may be in the high-risk group, performing screening tests and conducting advertising campaigns on television as well as placing content on posters posted in places such as clinics, workplaces or bus stops.

Conflict of interest
None

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