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Advances in Research on Risk Factors for Disease Progression in Advanced Prostate Cancer

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Abstract

Advanced prostate cancer has mostly lost the chance of surgery, and has a low 5-year survival rate and high mortality rate. Therefore, exploring the risk factors for advanced prostate cancer disease progression can help formulate scientific and standardized treatment plans and strategies for advanced prostate cancer disease progression. Intervention measures provide evidence to improve the quality of life and survival rate of patients. Based on the existing research reports at home and abroad, I reviewed the risk factors related to the progression of advanced prostate cancer.

Keywords: advanced prostate cancer, disease progression, castration-resistant prostate cancer, biochemical recurrence, local recurrence

1. Introduction

Prostate cancer is the most common malignant tumor in the male genitourinary system. According to the 2020 GLOBOCAN statistics of the World Health Organization (WHO), its incidence rate ranks second among all male malignant tumors worldwide, second only to lung cancer; Its death rate ranks fifth among all malignant tumors in men (Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A & Bray F., 2021). According to the American Cancer Society (ACS) statistics, in the United States, the incidence of prostate cancer accounts for the first male malignant tumors. In 2021, the number of new prostate cancer patients in the United States is expected to reach 248,530, accounting for 26% of all male malignant tumors; It ranks second among malignant tumors, and the number of new deaths will reach 34,130, second only to lung cancer (Siegel RL, Miller KD, Fuchs HE & Jemal A., 2021). The morbidity and mortality of prostate cancer in Asia are much lower than those in European and American countries (Zhu Y et al., 2021). China is one of the countries with relatively low incidence and mortality of prostate cancer. In 2015, the national incidence rate was 10.23/100,000 and the mortality rate was 4.36/100,000 (Zheng Rongshou, Sun Kexin, Zhang Siwei, et al., 2019). However, in recent years, its growth trend has been faster than that

of western developed countries. Moreover, due to factors such as the aging population and changes in diet structure in my country, the incidence and mortality of prostate cancer have shown an obvious upward trend (He Jie, Chen Wanqing, Li Ni, et al., 2022). In addition, because prostate cancer has no obvious clinical symptoms in the early stage and PSA screening in my country has not yet been popularized in primary medical institutions, and prostate cancer has the characteristics of strong tissue invasion and easy early metastasis, most prostate cancer patients in my country have already diagnosed when they are discovered. In the advanced stage or metastatic state (about 54% metastasized when diagnosed) (Chinese Anti-Cancer Association Urology and Genital Tumors Professional Committee, 2018; Prostate Cancer Group of Urology and Male Reproductive System Tumor Professional Committee of Chinese Anti-Cancer Association, 2017; Sun Yifei et al., 2022), most of them have lost the chance of surgery, which also makes the low 5-year survival rate and high mortality rate become the epidemic of prostate cancer in my country (Ji Hongli, Wang Mei, & Miao Peng, 2020). Based on the above understanding, in order to screen out the risk factors of advanced prostate cancer disease progression as early as possible and intervene early in the disease progression, the author makes a review on the risk factors of advanced prostate cancer disease progression.

Disease progression in prostate cancer is defined according to primary therapy as a component event reflecting discontinuation of delayed therapy, biochemical recurrence, local progression, or the emergence of distant metastases (Szulkin R et al., 2012). Since endocrine therapy is the main treatment for advanced prostate cancer, the early effect is more significant, but after 1-3 years, almost all patients progress to castration-resistant prostate cancer (Wang Qi, 2013; Zhang Hongyi et al., 2017; Xu Lei, 2007; Wang Lan, Li Hongjie, & Ma Zhifang, 2020). Therefore, we also included castration-resistant prostate cancer in the disease progression of prostate cancer.

2. Definition of Advanced Prostate Cancer

2.1 Locally Advanced Cancer

The tumor breaks through the prostate capsule, causing local spread and/or regional lymph node metastasis (T3-4Nx/+M0 and T1-2N+M0). The regional lymph nodes of prostate cancer are pelvic lymph nodes. It does not extend beyond the pelvic region, so it is a regional disease. Since the lesion is no longer limited, on the basis of the initial local/regional treatment, other adjuvant treatments are often required to better reduce tumor recurrence/control disease progression and improve patient survival. Including extraprostatic local tumor invasion or regional lymph node metastasis with positive imaging findings, staged cT3-4Nx/+M0, extraprostatic invasion and/or regional lymph node metastasis confirmed by pathology after radical prostatectomy, staged pT3- 4Nx/+M0 and T2N+M0.

2.2 Metastatic Cancer

The tumor has distant metastasis, accumulating non-regional (extraregional) lymph nodes, bones or other organs (TxNxM1a/b/c), and the disease has spread to other parts of the body, also known as systemic or systemic Diseases, mainly systemic treatment, local treatment is mostly palliative means.

3. Definition of Disease Progression

Disease progression in prostate cancer is defined according to primary therapy as a component event reflecting discontinuation of delayed therapy, biochemical recurrence, local progression, or the emergence of distant metastases (Szulkin R et al., 2012). Since endocrine therapy is the main treatment for advanced prostate cancer, the early effect is more significant, but after 1-3 years, almost all patients progress to castration-resistant prostate cancer (Wang Qi, 2013; Zhang Hongyi et al., 2017; Xu Lei, 2007; Wang Lan, Li Hongjie, & Ma Zhifang, 2020). Therefore, we also included castration-resistant prostate cancer in the disease progression of prostate cancer. In summary, Disease progression can be manifested as persistently elevated PSA levels (PSA progression) or imaging-visible tumor progression (imaging progression).

3.1 Progression of PSA

The serum PSA level was detected every other week for three consecutive times. At the same time, the absolute value of PSA is above 2mg/ml. Including castration-resistant prostate cancer (CRPC), biochemical recurrence (BCR), and biochemical recurrence includes BCR after radical prostatectomy (RP) and BCR after radical radiotherapy for prostate cancer.

3.1.1 CRPC

CRPC refers to prostate cancer whose disease continues to progress after continuous androgen deprivation therapy. Diagnosis of CRPC should meet the following two conditions at the same time: (1) Serum testosterone maintained below the castration level: that is, serum testosterone level <50ng/dl (or <1.7 nmol/L); (2) Biochemical progress: PSA value >2ng/L ml, with an interval of 1 week, for 3 consecutive times with an increase of >50% compared with the baseline; or imaging progress: 2 or more new lesions or soft tissue lesions that meet the solid tumor response evaluation criteria are enlarged on bone scan.

3.1.2 Biochemical Recurrence (BCR)

3.1.2.1 BCR After Radical Prostatectomy (RP)

After RP, the PSA value can generally drop below 0.2 ng/ml. If the PSA rises above 0.2 ng/ml in two consecutive follow-up visits with an upward trend, it is defined as RP After BCR or BCR.

3.1.2.2 BCR After Radical Radiotherapy for Prostate Cancer

PSA value after radical radiotherapy of prostate cancer is higher than the post-radiotherapy nadir of 2ng/ml, it is defined as biochemical recurrence after radiotherapy, regardless of whether other treatments are used at the same time, and regardless of the post-radiotherapy nadir PSA value.

3.2 Imaging Progress

New lesions were found in imaging examinations, including at least 2 new bone metastases on bone scan, or new soft tissue lesions evaluated by RECIST criteria. It includes local progression of distant metastasis and local recurrence, and local recurrence includes local recurrence after radical prostatectomy and local recurrence after radical prostatectomy.

3.2.1 Distant Metastasis

The tumor has distant metastasis, involving non-regional (extraregional) lymph nodes, bones or other organs, PET-CT, PET-MRI, PSMA PET/CT, bone ECT, mpMRI, etc. are optional Film degree exam.

3.2.2 Local Progression

The evolution from localized disease to regional disease not only means the expansion of the invasion range of cancerous tissue, that is, the spread in the local area around the prostate and the pelvic area; it also indicates the increase of the malignancy of the tumor.

3.2.3 Local Recurrence

3.2.3.1 Local Recurrence After Radical Prostatectomy (RP)

The judgment of local recurrence after RP mainly depends on residual imaging examination. The common sites of local recurrence are the urethrovesical anastomosis, the back of the original seminal vesicle and local lymph nodes.

3.2.3.2 Local Recurrence After Radical Radiotherapy of the Prostate

Cancer cells were found in prostate biopsy more than 18 months after radiotherapy, accompanied by an increase in PSA, but no evidence of metastasis was found in CT, MRI, bone scan or other imaging examinations.

4. Risk Factors for Disease Progression in Advanced Prostate Cancer

4.1 Age

Almost all prostates occur in men over the age of 50, and men under the age of 50 account for less than one in a thousand prostate cancer patients. Han Sujun et al (2013) investigated the current situation and prevalence trend of prostate cancer in my country from 1998 to 2008, and showed that the incidence of prostate cancer in men over 50 years old gradually increased with age, and the increase in incidence mainly occurred in Elderly patients over 60 years old, it can be seen that in the age composition of prostate cancer incidence, the proportion of the high age group has increased significantly, and it shows a continuous upward trend. Whether age is a risk factor for prostate cancer progression is still controversial. Gu Zhenhua et al (2017) found that prostate cancer bone metastasis is positively correlated with age, that is, the older you are, the higher the risk of bone metastasis. The results of retrospective analysis by Ji G et al. (2017) showed that compared with patients aged 55 to 75 years, men aged ≤55 years or >75 years showed a higher incidence of prostate cancer, and younger and older male patients. More likely to have more aggressive disease. Xiong Tailin et al. (2014) found that there was no statistically significant difference in the probability of developing CRPC within one year among the groups of patients <60 years old, 60-69 years old, 70-79 years old and ≥80 years old, and age may not be the reason for developing CRPC within one year. Influencing

factors, but errors caused by small sample data cannot be ruled out. Zhang Hongyi et al (2017) found no significant correlation between age and multiple metastases. This analysis aimed to determine the association between disease progression and age in advanced prostate cancer.

4.2 Gleason Score

The grading of prostate pathological specimens is of great significance for the prognosis of prostate cancer. At present, Gleason grading, Mostofi grading and MD Anderson hospital grading are the three most important grading systems. Among them, Gleason grading is widely used because of its high consistency in prostate biological behavior and prognosis, and is included by WHO (2004) and AJCC (2002) as an important pathological index for prostate cancer treatment. In 2014, the International Association of Urological Pathology (ISUP) revised its reporting system, and then updated it in 2017. While retaining the basic principles of the Gleason score, the original Gleason score was replaced with a new 1-5 group grading system, namely: 1 group (Gleason≤6 points); 2 groups (Gleason 3+4=7 points); 3 groups (Gleason 4+3=7 points); 4 groups (Gleason 4+4=8 points, Gleason 3+5=8 points, Gleason 5+3=8 points); 5 groups (Gleason 9-10 points). Domestic and foreign studies have found that Gleason score is a risk factor for prostate cancer disease progression. Zhang Hongyi et al. (2017) found that patients with higher Gleason scores are more likely to have multiple site metastasis, especially those with Gleason scores of 8-10; Xiong Tailin et al. (2014) found that patients with Gleason scores. The higher the value, the greater the risk of developing CRPC within 1 year; Lin et al (2019) showed that compared with group 1, the risk of developing CRPC in patients in Gleason 3, 4 and 5 groups was 3.169, 4.335 and 5.159 times higher, respectively, Gleason grading group is one of the risk factors for patients with metastatic prostate cancer (mPCa) to progress to CRPC, and the higher the Gleason grading group, the higher the risk of developing CRPC after endocrine therapy.

4.3 Clinical Staging

The staging of prostate cancer is an important basis for the formulation of prostate treatment plans. At present, TNM staging is recommended at home and abroad (T stands for tumor, N stands for lymph node, and M stands for metastasis). At present, the eighth edition of AJCC prostate cancer TNM staging system is mainly used. At present, domestic and foreign studies have found that clinical stage is the main factor of prostate cancer disease progression. Qu Yuanyuan et al (2013) found that clinical stage of prostate cancer is an important clinical indicator for evaluating biochemical recurrence after radical prostatectomy; Tan Guojun et al (2015) found that there is a positive correlation between prostate cancer clinical stage and serum PSA and PSAD, which can be used as an effective indicator to predict the prognosis of prostate cancer. However, due to the relatively small number of cases in this study, there may be some deviation in the statistics of clinical stage. Xiong Tailin et al., (2014) found that TNM stage is an independent risk factor for prostate cancer patients to progress to CRPC within 1 year. The later the clinical stage, the greater the risk of progressing to CRPC within 1 year. Therefore, for patients with advanced clinical stages, the higher the risk of disease progression, the more we need to adopt individualized treatment plans to prolong progression-free survival (Wang Lan, Li Hongjie, & Ma Zhifang, 2020).

4.4 Initial PSA Value

Prostate-specific antigen (PSA) is a protease containing 237 amino acids, which is secreted into the prostate duct system by the prostate epithelial cells and tissues around the urethra. Under normal circumstances, the basement membrane around the prostate duct system has a barrier function to prevent PSA from entering. In the blood system, the concentration of PSA in the blood is low, and prostate cancer, prostatitis, and prostate damage can destroy this barrier, allowing PSA to enter the blood system, causing serum PSA to increase, and the increase in PSA is even more severe when it becomes cancerous. It is obvious (Partin AW, Brawer MK, Bartsch G, et al., 2003); prostate cancer can damage the normal prostate structure, destroy the structure of blood vessels and lymphatic vessel walls in the prostate tissue, make PSA diffuse into the blood circulation system, and cause the increase of serum PSA level, and the lower the degree of differentiation. The more aggressive the prostate cancer, the stronger the damage to the barrier, resulting in more PSA entering the blood. Zhang Hongyi et al (2017) found that initial serum PSA was significantly correlated with multiple metastases, and patients with serum PSA level >

60ng/ml before treatment were more likely to have multiple metastases. Nayyar et al. (2010) and Tomioka et al. (2014) showed that a higher PSA baseline level was associated with a shorter time to CRCP; however, with the deepening of the research, some people also put forward the opposite opinion. Xiong Tailin et al (2014) Studies have found that as the differentiation of prostate cancer cells deteriorates, the normal acinar structure in the prostate disappears, the glands fuse into solid tumor cells, and the lack of glandular cavity structure leads to less or no secretion of PSA. The PSA value measured in this type of prostate cancer patients may not be high or be in the normal range. Yamamoto et al (2001) also found in their study that compared with the usual types of M1 prostate cancer, cases of M1 prostate cancer with PSA less than 10 ng/mL are almost always poorly differentiated or undifferentiated, which is different from common M1 prostate cancer with multiple differentiations. In stark contrast, because of this, these cancers had lost the characteristics of the original prostate tissue, and the release of PSA into the blood was disproportionate to the extent of the cancer. Therefore, the initial PSA value should be comprehensively evaluated in combination with the patient's clinical stage and pathological examination.

4.5 Minimum PSA Value (nPSA)

Since the initial PSA value is still controversial as a risk factor for evaluating the progression of prostate cancer, more and more scholars consider looking for new indicators to evaluate the progression of prostate cancer by dynamically observing the changes in PSA during ADT treatment, therefore, the index that PSA reached the lowest value after ADT treatment was developed and recognized by the majority of scholars, and it is regarded as an important index for evaluating the prognosis after endocrine therapy. Lin et al (2019) and Tomioka et al (2014) found that patients with higher nPSA had shorter progression-free survival (PFS) after ADT treatment and a higher risk of developing CRPC. Kwak et al (2002) considered that nPSA levels after hormone therapy may be the most accurate factor for predicting the progression of hormone-refractory prostate cancer, and a lower limit of nPSA levels of 1.1 ng/ml provided the best sensitivity and specificity. Sasaki et al (2011) researched that prostate cancer tissue may be composed of hormone-sensitive and hormone-resistant prostate cancer cells, and the ratio of the two cells varies from patient to patient. ADT treatment only inhibited the AR mediation in hormone-sensitive prostate cancer cells. Therefore, patients with higher nPSA mean a higher proportion of hormone-resistant prostate cancer cells, less effective ADT treatment, and a higher risk of disease progression. Therefore, it is particularly important to screen out patients with high nPSA as early as possible and to carry out effective treatment (such as radiotherapy, chemotherapy, etc.) to prolong the progression-free survival (PFS) of patients.

4.6 Time to Reach the Minimum Value of PSA

Like nPSA, the time to reach the lowest value of PSA is also an indicator derived from the dynamic observation of PSA, and is now widely used to predict the progression of prostate cancer. At present, a large number of studies at home and abroad have shown that the disease progression of patients with PSA reaching the lowest value > 9 months is later than that of patients with CRPC ≤ 9 months. Lin et al. (2019) and Tomioka et al (2014) showed that the time to reach the lowest value of PSA is a risk factor for the progression of prostate cancer to CRPC, and the shorter time to reach the lowest value of PSA, the higher risk of progression to CRPC after ADT. Sasaki et al (2011) believed that the rapid apoptosis of hormone-sensitive prostate cells caused by ADT treatment may create an environment conducive to the growth of hormone-resistant prostate cancer cells, leading to their rapid proliferation and progression to CRPC. Therefore, in clinical practice, attention should be paid to patients whose PSA reaches the lowest value ≤ 9 months after ADT treatment, and a reasonable treatment plan should be formulated as soon as possible.

4.7 Alkaline Phosphatase (ALP) Level Before Treatment

More than 90% of advanced prostate cancers have bone metastases, while 95% of prostate cancer bone metastases are osteogenic lesions, 5% are mixed lesions, and simple osteolytic lesions are rare (Roudier MP et al., 2008). The main sources of ALP are the liver and bones. Bone-specific ALP (bALP) accounts for 40-50% of ALP levels in healthy adults. bALP is an enzyme expressed on the surface of osteoblasts. Elevated levels may indicate an ongoing disease in the bone. Therefore, in the absence of

extensive liver disease, bALP is a major component of total serum ALP levels in prostate cancer bone metastases, and measurement of ALP levels can reflect osteoblast activity and disease extent in patients with bone metastases (metastatic volume) (Roudier MP et al., 2008). Mao Jinlei et al. (2014) found that serum ALP>1000Lg/L is a risk factor for the outcome of positive bone metastasis on bone scan and has predictive value. Mori et al. (2020) found that elevated serum alkaline phosphatase levels were associated with increased risk of overall mortality and disease progression in patients with hormone-sensitive prostate cancer through a meta-analysis. Independently associated with overall survival in patients with sensitive prostate cancer. Lv et al (2017) showed that the higher the ALP level before treatment, the shorter the event of prostate cancer progressing to CRPC. However, Chen Xi (2010) believed that since ALP not only reflects diseases of the skeletal system, but also diseases of the liver and gallbladder system. It is not enough to detect alone, and it is more suitable for joint detection with other indicators. In summary, ALP is a risk factor for prostate cancer bone metastasis and disease progression, but because of its low specificity, we can use it in combination with other indicators. Sufficient attention should be paid to these patients, and individualized treatment plans should be adopted to slow down the progression of the disease.

4.8 Bone Metastases (BM) or Visceral Metastases

In advanced prostate cancer, more than 90% of patients developed bone metastases, leading to a significantly shortened median survival event (2022). Most patients with bone metastases from prostate cancer are not discovered in the early stage due to no obvious clinical symptoms, and patients are often discovered when the disease progresses and leads to bone pain, limb movement impairment or pathological fracture (Sturge J, Caley MP, Waxman J, 2011). Bone metastases in prostate cancer mainly occur in the pelvis and spine, while skull metastases are less common. Among the peripheral bones, the probability of femoral metastases is higher than that of extremities (Coleman RE, Croucher PI, PadhaniAR, et al., 2020). In addition, bone metastasis of prostate cancer can also cause many skeletal-related events (SRE), such as pathological fractures, hypercalcemia, spinal cord compression, and even paraplegia, which seriously deteriorate the quality of life and prognosis of patients (Akaza, H., 2011). In the CHAARTED study, bone metastases of prostate cancer were divided into high-volume clisease (HVD) and low-volume clisease (LVD). Outside the spine or pelvis; LVD definition: no visceral metastases and no more than 3 bone metastases. The 2020 AUA/ASTRO/SUO and other guidelines recommend that in newly diagnosed metastatic hormone-sensitive prostate patients, clinicians should assess the degree of disease metastasis (high burden or low burden). Several large-scale clinical studies also consider high risk disease (HRD) if two of the following three factors are met, namely: Gleason score ≥ 8, bone metastases ≥ 3, and visceral metastases. Howard et al. (2016) showed that the more bone metastases before ADT started, the earlier the progression of CRPC. Sureka SK, Maheshwari R, Agnihotri S, et al. (2016) found that the time of patients entering CRPC was related to the degree of bone involvement. The median time of CRPC in prostate cancer patients ranged from 10 to 16 months, depending on the number of lesions on bone scan. Patients were found to go into CRPC earlier. It can be seen that the number and location of prostate cancer bone metastases are of great significance to the progression of advanced prostate cancer. For patients with HRD and HVD, multidisciplinary treatment or ADT combined with chemotherapy or Abiraterone or Enzarumide can reduce the disease progression and risk of death.

4.9 Prostate Volume

Anatomically, the prostate can be divided into peripheral zone, central zone and transition zone. The prostate transition zone is the smallest area in the prostate, accounting for about 5%-10% of the prostate gland components, and the central zone accounts for about 25% of the gland components. The peripheral zone is the largest component of the prostate, accounting for about 70% of the glandular components. Prostatic hyperplasia is more likely to occur in the transition zone, while 80%-85% of prostate cancers are more likely to occur in the peripheral zone of the prostate. Guzman et al (2019) considered that benign prostatic hyperplasia leads to decreased glandular density and increased capsular thickness in the peripheral region, and compression-induced loss of blood flow due to direct pressure-related tissue damage and expansion of the transitional zone in growing benign prostatic hyperplasia. Atrophy and fibrosis of glandular tissue in the

peripheral area, thereby reducing the incidence of prostate cancer. Yamashiro et al (2021) found 41 articles reporting an inverse (negative) relationship between prostate volume and prostate cancer incidence through a systematic review over the past 30 years, and 39 of the 41 articles (95%) showed a statistically significant inverse relationship. Therefore, the volume of the prostate may be closely related to the incidence of prostate cancer. The smaller the prostate, the higher the incidence of prostate cancer. However, whether the prostate cancer with smaller prostate volume increases the risk of prostate cancer disease progression is not yet clear.

4.10 Perineural Infiltration (PNI)

PNI, the process by which tumors invade nerves, is an underappreciated route of metastatic spread, a marker of poor outcome, and a harbinger of decreased survival (Liebig C, Ayala G, Wilks JA, Berger DH, & Albo D., 2009). It is also a well-recognized mechanism for the spread of cancer cells beyond the prostate through the abundant innervation of the posterior portion of the gland (ENDRIZZI J & SEAY T., 2000; Bonin SR, Hanl, Lee WR, Movsas B, Al-Saleem Ti, & Hanks Ge, 1997) showed that PNI was a significant predictor of biochemical failure in 484 prostate cancer patients who received radiation therapy. Patients with PSA levels ≤ 20 ng/mL and PNI in biopsy were free of PNI at 3 and 5 years. The progression-free survival rates were 65% and 39%, respectively, while the 3-year and 5-year progression-free survival rates were 88% and 65% for those with PSA levels ≤ 20 ng/ml and no PNI, respectively, and the difference was statistically significant. Loeb et al (2010) found that PNI was significantly associated with aggressive pathology and biochemical progression. Multivariate analysis showed that PNI was significantly associated with prostatic extension and seminal vesicle invasion. Biochemical progression occurred in 10.5% of PNI patients without PNI. Only 3.5% of patients. Bai Junbo et al. (2021) found that PNI is an adverse prognostic factor for the progression of prostate cancer to castration-resistant prostate cancer after regular endocrine therapy. The probability of castration resistance in patients with PNI is 2.263 times that of patients without PNI; found that the more the number of PNI lesions, the shorter the time of biochemical recurrence; Zhu Yinjie et al. (2016) showed that PNI is of great significance in predicting biochemical recurrence, and can be used as an important indicator for predicting biochemical recurrence after radical prostatectomy. If PNI was found, indicating that the risk of biochemical recurrence increased by 1.664 times. In summary, PNI is an important predictor of prostate cancer progression and prognosis. When PNI is found after prostate biopsy or radical prostatectomy, especially when the number of PNI is large, we need to formulate and adjust individualized treatment plans and strengthen detection PSA, pay attention to the preoperative PSA level and Gleason score, etc., and give adjuvant treatment as soon as possible.

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