International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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# The pathophysiologic basis of prostate cancer review

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International Journal of Science and Research Archive, 2022, 07(01), 213–219

Publication history: Received on 25 August 2022, revised on 01 October 2022, accepted on 04 October 2022

Article DOI: https://doi.org/10.30574/ijsra.2022.7.1.0205

## Abstract

Worldwide, prostate cancer is the most commonly diagnosed malignancy and the sixth leading cause of cancer death in men. Diagnosis is primarily based on prostate-specific antigen (PSA) testing, MRI scans, and prostate tissue biopsies, although PSA testing for screening remains controversial. New diagnostic technologies including risk stratification bioassay tests, germline testing, and various PET scans are now available. When the cancer is limited to the prostate, it is considered localized and potentially curable. If the disease has spread outside the prostate, bisphosphonates, rank ligand inhibitors, hormonal treatment, chemotherapy, radiopharmaceuticals, immunotherapy, focused radiation, and other targeted therapies can be used. This activity is a current, comprehensive review of the evaluation and management of patients with prostate cancer and highlights the role of the interprofessional team in improving care for affected patients. Metastatic castration-resistant prostate cancer (mCRPC) remains a terminal diagnosis with an aggressive disease course despite currently approved therapeutics. Despite many recent advances in the therapy for metastatic castration-resistant prostate cancer (mCRPC), the disease remains incurable, although men suffering from this disease are living considerably longer.

**Keywords:** Metastatic prostate cancer; Castration-resistant prostate cancer; Prostate-specific membrane antigen (PSMA); Polyadenosine diphosphate [ADP]-ribose polymerase (PARP) inhibitor; Androgen receptor inhibitors (ARIs)

## 1. Introduction

Worldwide, prostate cancer is the most commonly diagnosed male malignancy and the fourth leading cause of cancer death in men [1]. This amounted to 1,414,249 newly diagnosed cases and 375,000 deaths worldwide yearly from this disease in 2020 [2]. Globally, prostate cancer is the most commonly diagnosed malignancy in more than fifty percent of countries (112 of 185). Fortunately, most prostate cancers tend to grow slowly and are low-grade with relatively low risk and limited aggressiveness [3]. Prostate cancer (PC) is the second most commonly diagnosed cancer among men worldwide, following lung cancer, and the first among men in the USA [2-3]. Although clinical outcomes are excellent for patients with localized disease, patients with metastatic prostate cancer (MPC) have poor prognosis, with a 5-year survival rate reaching 30%. Androgen deprivation therapy (ADT) has long been the treatment of choice as backbone of all other therapies, by reducing circulating androgens to castration levels and slowing the progression of the disease [4].

When the cancer is limited to the prostate, it is considered localized and potentially curable [5].

If the disease has spread to the bones or elsewhere outside the prostate, pain medications, bisphosphonates, rank ligand inhibitors, hormonal treatment, chemotherapy, radiopharmaceuticals, immunotherapy, focused radiation, and other targeted therapies can be used. Outcomes depend on age, associated health problems, tumour histology, and the extent of cancer [6].

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## 2. Epidemiology and aetiology

Prostate cancer is the second most common cause of cancer deaths in men in most developed countries, and the incidence has increased significantly over recent years [6]. In the United States the lifetime probability of developing prostate cancer is one in six. In 1997 more than 209 900 American men were diagnosed with prostate cancer and more than 41 800 died from the disease [7]. In England and Wales death rates have trebled over the last 30 years, one in 13 men is affected, and 20 000 cases are diagnosed each year [7].

Age is the most important risk factor. Prostate cancer is rare under the age of 40, and its incidence increases exponentially with age [8]. There is a varied geographical incidence. The age standardized mortality rates vary from 0.1 per 100 000 in Thailand to 30 per 100 000 in some parts of the West Indies. Studies of migrant populations have suggested that environmental factors are at least as significant as race [9]. Environmental factors implicated in prostate cancer include a high intake of saturated fat and low level of dietary selenium, vitamin E, and vitamin D [7-9]. Radiation exposure may be important. In an analysis of deaths among 39 546 employees of the United Kingdom Atomic Energy Authority the only malignancy clearly related to radiation exposure was prostate cancer [9].

It is estimated that less than 5% of all prostate cancer is hereditary. The risk of prostate cancer is increased by a factor of 1.3 if there is an affected father in the family, and by a factor of 2.5 if there is a brother who has prostate cancer [7-9].

Prostate cancer is thought to arise after a sequence of at least eight genetic mutational events. Early events appear to be the loss of tumour suppressive genes such as p53 which is mutated in up to 64% of tumours and p21 in up to 55%.[8] The recently identified p73 tumour suppressor gene has significant homology to p53 and also appears to be mutated in prostate cancer.[8] MMAC1/p10, however, is the most widely mutated tumour suppressor gene in prostate cancer and may contribute to the acquisition of the metastatic phenotype [10]. The development of the hormone refractory phenotype appears to be related to the over expression of mutant p53 and bcl-2 family of proteins as well as amplification of the androgen receptor [10-11].

## 3. Pathology

Approximately 95% of all prostate cancers are adenocarcinomas. Roughly 4% of all prostate malignancies arise from the transitional epithelium of the urethra or ducts as transitional cell carcinoma. Primary carcinoid tumours of the prostate, sarcomas, and primary small cell carcinomas of the prostate are rare. Tumours of other organs may spread into the prostate [11-12].

Histological recognition of prostate cancer depends on the overall assessment of the architecture and upon the cytology of individual cells. The prostate cancer cell cytoplasm may contain large amounts of acid phosphatase and prostate specific antigen (PSA) [12]. Using immunohistochemistry for these antigens it is possible to differentiate prostatic carcinoma cells from other tumour cells. Grading is based on glandular differentiation and the system most commonly employed is the Gleason method [13].

## 4. Diagnosis

Fewer than 10% of patients with prostate cancer are diagnosed at screening assessments in the UK, and the vast majority are diagnosed because of their presentation with symptoms. The diagnosis must be confirmed by histological examination of the prostatic tissue. Transrectal biopsy is widely favored. Fine needle aspiration cytology as a means for diagnosis has not gained widespread popularity probably due to its limited sensitivity when compared with needle biopsy [14]. PSA is an effective tumour marker in prostate cancer, but its use as a screening tool in the early detection of prostate cancer is controversial [14].

Computed tomography of the pelvis is currently the most commonly employed imaging modality for assessing the extent of local spread of prostate cancer. Despite initial enthusiasm, the use of transrectal ultrasound has not proven to be more useful at determining seminal vesicle involvement or extracapsular spread than digital rectal examination [14-15]. Magnetic resonance imaging (MRI) appears to have equal sensitivity to computed tomography for detection of pelvic lymph node involvement [16].

Bone scans are used routinely and have a false negative rate of 11%. MRI is the most sensitive technique for detecting bone metastases in prostate cancer but it is limited by its relative inability to image the whole skeleton [17].

## 5. Adjuvant therapy of localised prostate cancer

The role of hormonal therapy has been investigated in patients with localized tumours with the aim of improving disease control in patients treated with radiotherapy [17]. Hormonal treatment before definitive local therapy leads to a significant change in size of the neoplastic prostate gland reducing the radiotherapy planning target volume of the prostate by 30%–40% and thus may potentially reduce morbidity. Recent clinical studies have shown the benefit of combined hormone and radiation therapy in terms of local control and biochemical disease-free survival [18]. There is in addition now emerging evidence of a benefit in overall survival, though more data is needed here [18-19].

The results of radical prostatectomy and external beam radiotherapy are poor in patients with locally advanced disease. After prostatectomy, 54% of patients with capsular penetration and low-grade tumours remain free of biochemical relapse at 10 years, while only 42% with high grade tumours are disease free [19]. Ten-year survival rates in patients with locally advanced disease treated with radiotherapy are between 35% and 45%. Trials have shown that a combination of hormonal treatment and external beam radiotherapy is better than radiotherapy alone in terms of overall survival at five years for patients with locally advanced prostate cancer [20].

In patients with evidence of extracapsular disease after radical prostatectomy and raised PSAs, salvage external beam radiotherapy has been advocated by some groups with complete PSA responses reported in 10%–55% of patients [19-20]. Other groups have advocated early hormonal treatment for these patients. Further trials are warranted as no consensus exists [21].

## 6. Primary therapy of advanced tumours

The gonadotrophin releasing hormone (GnRH) analogues have similar response rates and effect on overall survival as older forms of hormone therapy such as orchidectomy and oestrogen derivatives [21]. In view of the cardiovascular morbidity associated with oestrogen derivatives and the relative unacceptability of bilateral orchidectomy, GnRH analogues should be first line treatment for patients with metastatic prostate cancer. These compounds are stimulatory in the initial phase of treatment and as a result may give rise to an acute exacerbation of tumour symptoms and signs [22]. This can be avoided by antiandrogens given to the patient before and continued for 2–3 weeks after the initiation of GnRH agonist therapy. One- and three-monthly depot preparations are currently available. Adverse effects of GnRH analogues include tiredness and hot flushes. It has been argued that oestrogen therapy should be prescribed because it is cheap. However, you get what you pay for and the cardiovascular toxicity of oestrogens is not abrogated by low dose aspirin [23]. Diethylstilbestrol will also cause indigestion in one third of patients and gynecomastia, which may not be prevented by irradiation of the breast bud [23].

Antiandrogens can be used as first line or second line treatments in metastatic prostate cancer. Cyproterone acetate was the first drug in this class used for the treatment of prostate cancer. Although it inhibits the androgen receptor, its primary activity is progestogenic. In clinical trials cyproterone acetate was found to be equivalent to oestrogen derivatives such as diethylstilbestrol in response rate and overall survival. The first pure antiandrogen to enter clinical practice was flutamide [24]. Its principle side effects include gynecomastia, fatigue, diarrhea, and hepatotoxicity. The incidence of hot flushes and impotence are significantly less than with castration. Bicalutamide has the advantage of once-a-day dosage [24].

## 7. Improving survival

The hormonal treatment of metastatic prostate cancer is not curative and associated with a median duration of PSA response of only one year [25]. Subsequently, several strategies have been developed to try and improve survival. Combined androgen blockade is based on the principle of eliminating all sources of androgen (that is adrenal, dietary, and testicular). Several trials have been conducted using a variety of antiandrogens with medico surgical castration over the past decade. In the year 2000, the Prostate Cancer Triallists' Collaborative Study Group published their meta-analysis of all available trials, which showed a 2.3% improvement in survival with the use of flutamide but no other antiandrogens, but at an increased incidence of gastrointestinal toxicity [26]. This analysis failed to describe median survival. Most prospective randomized studies have shown a seven-month survival advantage with combination treatment [25-26].

Intermittent androgen blockade involves medical castration until the PSA reaches a nadir followed by discontinuation of the GnRH agonist with recommencement when the PSA rises to a specific level [26]. This approach potentially reduces toxicity and cost of treatment, as well as possibly delaying the development of hormone resistance. Early clinical trials

using this approach have demonstrated its clinical feasibility. However, results of randomized comparisons with continuous androgen ablation are awaited [27].

Sequential androgen blockade employs the use of newer agents such as finasteride with conventional antiandrogens. Finasteride is a 5-alpha reductase inhibitor which prevents conversion of testosterone to dihydrotestosterone, which has a 10-fold higher affinity for the androgen receptor. Early studies have demonstrated a 30%–40% fall in PSA levels with finasteride given as a single agent [28]. This is significantly worse than response rates with antiandrogens or castration. However, it is hoped that combining finasteride with antiandrogens such as flutamide and bicalutamide will give rise to synergistically enhanced benefit, and clinical trials to evaluate this approach are currently in progress [28-29]. Chemotherapy for prostate cancer has been disappointing. Single agent treatment with cyclophosphamide, methotrexate, or anthracyclines gives modest response rates. The newer agent, mitozantrone, has shown a clear advantage in one study as an adjuvant treatment in localized prostate cancer[30]. The use of chemotherapy in conjunction with hormone treatment in advanced or metastatic cancer has been limited. There is no consensus emerging from the trials with some showing a minor improvement in response rates but no survival advantage, while others fail to show any advantage [30]. However, improved palliation of symptoms was shown by using the combination of mitozantrone and prednisolone compared with prednisolone alone [30].

## 8. Treatment of relapsed prostate cancer

It is believed that at presentation prostate cancers contain heterogenous populations of hormone sensitive and hormone resistant cells. Treatment with hormonal therapy is eventually accompanied by the selective growth of hormone resistant clones. Biochemical relapse occurs after a median duration of remission of about one year with symptom progression two years later [31]. At symptomatic relapse the median duration of survival is 6–8 months [31].

A number of second line hormonal therapies have been evaluated in patients with relapsed prostate cancer after initial medical or surgical castration. In patients who have been treated with combined androgen blockade, it is recognized now that withdrawal of the antiandrogen may be associated with a response in 10%–40% of patients with a median duration of response of three months [32]. The addition of an antiandrogen at relapse in those treated with GnRH agonist or surgical castration alone results in responses of 5%–15%. Glucocorticoids, such as hydrocortisone, can be used to suppress testosterone levels. In a phase III study of glucocorticoid therapy hormone refractory prostate cancer patients showed response rates of 20% with significant improvement in quality of life over patients managed with best supportive care, but no survival benefit was observed [33].

Radiotherapy has an important part to play in the treatment of painful bone metastases. When there is a single area of bone pain the choice is between a standard course of treatment of approximately 35 Gy over two weeks or a single large fraction of 8 Gy. Palliation of multiple areas of bone pain may be achieved by hemi body irradiation which occurs in two stages. Initially a single 6 Gy fraction is delivered to the upper half of the body and the same dose is administered six weeks later to the bottom half [34]. More recently, strontium has emerged as an alternative to hemi body irradiation. Strontium localizes to the bone and the treatment is generally well tolerated. Its use though is limited by cost [34-35].

## 9. Screening for prostate cancer

The relative benefits and costs of screening for prostate cancer is currently most contentious. The medical profession, for the main, feels that on the basis of the evidence presented there is not advantage to screening because the PSA test does not distinguish between benign and malignant disease, and there has been no proof that early treatment leads to increased cure rates [35]. The non-medical laity do not accept this and argue that logically early detection of cancer must offer an advantage. Two prerequisites must be met for screening to be a viable proposition in malignancy: (1) a test must be available which can diagnose the condition at a treatable stage, and (2) early diagnosis and treatment should lead to a reduction in disease mortality [36].

Digital rectal examination alone is insufficient for screening as its positive predictive value is only 11%–26% [37]. Transrectal ultrasound by its own also has been shown to be an unreliable screening method because of the high rate of false negative and false positive results. Much interest has focused on serum PSA as a screening tool. PSA is prostate specific but not cancer specific. It can also be raised in prostatitis and in 30% of patients with benign prostatic hypertrophy. Complicating matters further is the finding that only about two thirds of men with localized prostate cancer have a raised PSA, though it is increased in 95% of metastatic prostate cancer patients. When the serum PSA is 4–10 ng/ml about 20% of men will have positive biopsies, which increases to 50% if the level is greater than 10 ng/ml. screening with a combination of digital rectal examination and serum PSA may enhance detection efficiency [37-38].

## 10. Screening for prostate cancer

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## 11. Conclusion

Prostate cancer diagnosis and treatment can be complex and is often controversial. an interprofessional team of specialty-trained nurses, nurse practitioners, physician assistants, primary care providers, oncologists, radiation therapists, genetic counsellors, and urologists must work together to manage. These and many more issues continue to challenge clinicians who deal with prostate cancer patients and men at risk for this common, potentially lethal male malignancy. The interprofessional team can optimize the treatment of these patients through communication and coordination of care. Primary care providers, urologists, oncologists, radiation oncologists, and nurse practitioners provide diagnoses and care plans. Specialty care urologic nurses should work with the team to coordinate care and be involved in patient education and monitoring compliance. The interprofessional team can thus improve outcomes for patients with prostate cancer.

## Compliance with ethical standards

### *Acknowledgments*

We gratefully acknowledge University of Central Lancashire for Science and technology for providing the financial support and required facilities to carry out this research work through a scientific research grant.

### *Disclosure of conflict of interest*

All authors declare that they have no conflicts of interest.

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