

Prostate Cancer for the Internist

Shikha Jaiswal, Rehan Sarmad, Sumant Arora, Radhikha Dasaraju, Komal Sarmad¹

Department of Internal Medicine, University of Alabama at Birmingham, Montgomery Internal Medicine Residency Program, AL, 36116, ¹PGY-2, Department of Internal Medicine, West Virginia University, Morgantown, West Virginia, 26505, USA

Abstract

In the United States, approximately 240,000 men are diagnosed annually with prostate cancer. Although effective treatment options are available for clinically localized cancer, the potential burdensome co-morbidities and attendant healthcare costs from over diagnosis and over treatment have escalated the discussion and controversy regarding appropriate screening, diagnosis, and optimal management of prostate cancer. Although the lifetime risk of developing prostate cancer is approximately 1 in 6 (~16%), the risk of dying from the disease is only ~2%. The discrepancy between the cancer incidence and lethality has led to widespread scrutiny of prostate cancer patient management, particularly for low-grade, low-stage (indolent) disease. The vast majority of men diagnosed with clinically localized prostate cancer are treated with interventional therapies despite studies demonstrating that even without treatment, prostate cancer-specific mortality is low. A MedLine/PubMed search was performed using PICO format (Patient, Intervention, Comparison and Outcome) identifying all relevant articles. No restrictions were used for publication dates. The terms “Prostate Cancer”, “Screening”, “Mortality”, “Morbidity” yielded 307 results. “Diagnosis”, “Prognosis” and “Survival” yielded 1504 results. Further filters were applied to narrow down the results using keywords “Prostate cancer screening guidelines 2014”, “Beyond PSA”, “NCCN Guidelines prostate”, “MRI guided Prostate biopsy” yielding 72, 274, 54 and 568 results respectively. Of these, approximately 137 articles were found relevant and were reviewed. References from the reviewed articles were included in the final article.

Keywords: Androgen deprivation therapy, screening, prostate cancer, prostate specific antigen

Address for correspondence: Dr. Shikha Jaiswal, Department of Internal Medicine, University of Alabama at Birmingham, Montgomery Internal Medicine Residency Program, AL, 36116, USA. E-mail: shikhajaiswal@uabmc.edu

Introduction

Prostate cancer (PCa) is the most common nonskin cancer among men in the United States and is the second most common cause of cancer-related deaths. According to surveillance, epidemiology, and end results cancer statistics review, it is rare before 50 years of age with very few men dying before the age of 60 years.^[1] Most of the patients have a good prognosis even without treatment, but some cancers are aggressive. Old age is the strongest risk factor and about seventy percent of deaths due to PCa occur in patients older than 75 years. Black men and those with a family history have increased the risk of developing and dying from PCa. An estimated 233,000 new cases of

PCa will be diagnosed in 2014 and researchers predict that 29,480 of these cases will result in death.^[2]

Screening for Prostate Cancer

Screening for PCa remains a dilemma due to the potential of overdiagnosis and overtreatment with no significant mortality benefit. The evidence for screening remains controversial and guidelines vary among different medical organizations. Two landmark trials that assessed the benefits of screening are the European Randomized Study of Screening for Prostate Cancer

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(ERSPC) and prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial. The ERSPC study used data from seven centers in Europe and found a reduction in PCa deaths to 1/1000 men screened in men aged 55-69 years. It also showed relative risk reduction in PCa death rate by 20%, and reduction in metastatic cancers in the screened group by 41%; but with a risk of overdiagnosis.^[3] In PLCO trial, 76,693 men at 10 US study centers were studied from 1993 to 2001. Men in the screening group were randomly assigned to receive either annual prostate-specific antigen (PSA) screening for 6 years or digital rectal exam (DRE) for 4 years and controls received usual care. After 7-10 years follow-up, the death rate from PCa was very low and did not differ between the two groups.^[4] In a reanalysis of PLCO, considering comorbidities, PSA screening in men with good health showed reduced prostate specific mortality with minimal risk of over treatment.^[5] However, in a recently published 13 years follow-up results of the PLCO trial, no mortality benefit was found with organized screening compared to opportunistic screening and there was no interaction with age, baseline comorbidity, or pretrial PSA testing.^[6] Several other randomized trials have been published but the controversy on screening continues due to concerns over statistical analysis, insufficient follow-up time, different levels of PSA used as a cut off, different screening intervals, and contamination of control groups.

The American Cancer Society recommends that asymptomatic men with at least a 10-year life expectancy should have an opportunity to make an informed decision about screening for PCa after they receive information about the uncertainties, risks, and benefits associated with screening. Men with average risk should receive this information at 50 years and those at high risk, African-American men and those with the family history of PCa in men <65 years, should receive this information before 50 years of age.^[7]

The National Comprehensive Cancer Network (NCCN) guidelines recommend baseline DRE and PSA between ages 45 and 49. If serum PSA values are below 1 ng/mL, additional testing may be deferred until age 50 years. For men with PSA exceeding 1.0 ng/mL, testing should occur at 1-2 years interval, as this is above the 75th percentile for younger men (<50 years).^[8]

The American Urologic Association does not recommend routine screening in men aged 40-54 at average risk (recommendation; evidence strength Grade C). Screening intervals of 2 years preserve most of the benefits and reduces overdiagnosis and false positives (option; evidence strength Grade C)^[9]. [Table 1].

Table 1: Summary of prostate cancer screening recommendations from major organizations

NCCN	Informed decision making with all patients Baseline DRE and PSA at 45-49 years Repeat screening at 1-2 year intervals if PSA >1 ng/mL Annual screening from 50 years
American Cancer Society	Informed decision making for those who wish to be screened Screen men at average risk at 50 years of age with PSA±DRE Screen men with higher risk (African-Americans and those with a first degree relative with prostate cancer before 65 years age) at 45 years Men with multiple family members with prostate cancer before 65 years should receive this at 40 years No screening for men >75 years
American Urological Association	Informed discussion with all patients No routine screening in men at average risk between the ages 40-54 Screening stopped at 75 years but may be continued if life expectancy >10 years

PSA = Prostate specific antigen, DRE = Digital rectal examination, NCCN = National Comprehensive Cancer Network

Until we have better tests which have the ability to distinguish between indolent and aggressive cancer and there is agreement in guidelines between major professional organizations, patients, and physicians should be encouraged to engage in shared and informed decision process concerning screening for PCa.

Diagnosis

Biomarkers

DRE and serum tumor markers such as PSA are the mainstay of diagnosis. PSA is a glycoprotein secreted by prostate epithelial cells and was initially used to evaluate treatment response in men with PCa.^[10] It was first introduced as a screening test for PCa in the 1990s and is useful in diagnosis, staging, monitoring response to treatment, and detecting recurrence of PCa. It is mostly confined within prostatic ducts, but cancer cells secrete PSA into the blood stream by the disruption of the basement membrane. PSA produced by cancer cells binds avidly to serum proteins resulting in the lower percent of free PSA (fPSA), which is being studied as a screening tool. PSA density (PSA level divided by prostate volume), percentage free PSA (%fPSA), PSA velocity (rate of increase overtime), and PSA doubling time are useful to predict disease severity and behavior.^[10] PSA levels poorly correlate with disease and the optimal upper limit of the normal range is unknown. Abnormal cut-offs have been defined from 2.5 to 4 µg/l. Men with PSA <4 can have PCa, but the prevalence seems to be high with higher PSA levels.^[11] PSA can be increased

in benign prostatic hyperplasia, prostatitis, and recent ejaculation, procedures such as DRE, urinary bladder catheterization, and prostate biopsy.

In the last 2 years, a number of new, exciting biomarkers have emerged that offer the opportunity to assist clinicians in determining when to biopsy, whom to re-biopsy, and how to assist patients in their treatment decisions. PCa antigen 3 (PCA3) is a noncoding messenger RNA that has been shown to be elevated in >90% of men with PCa, but not significantly elevated in normal prostatic glands or even in benign prostatic hypertrophy. Urine PCA3 measurements have consistently added to the diagnostic information obtained from the PSA test. A particularly important attribute of PCA3 is the fact that, unlike PSA, urine PCA3 levels are independent of prostate size. In 2012, PCA3 was approved by the FDA as a diagnostic test for PCa in the setting of a prior negative prostate biopsy.^[12,13]

Recently, fPSA was found to include several sub forms, such as a precursor form of PSA (proPSA). PSA has a 17-amino acid leader sequence (preproPSA) that is cleaved to generate an inactive precursor protein (proPSA) with seven additional amino acids compared to mature PSA. Thus, theoretically, seven isoforms of proPSA should exist, although only (-1), (-2), (-4), (-5), and (-7) proPSA have been found. Of these (-2) proPSA (p2PSA) is the most stable form. Notably, p2PSA was found to be elevated in peripheral gland cancer tissue and to be specifically higher in serum from patients with PCa. Hence, it is a more cancer-specific PSA isoform. However, p2PSA had limited additional value in identifying aggressive PCa (GS \geq 7). Because p2PSA appears to have the highest predictive ability when associated with other variables, prostate health index (PHI) was developed. It is a mathematical algorithm that is defined as: $(p2PSA/fPSA) \dots \sqrt{PSA}$. Fifteen studies have investigated the utility of PHI and p2PSA. PHI has been found to have the highest predictive ability, followed by %p2PSA and %fPSA. Several authors have shown that PHI correlates with the Gleason Score and might result in the avoidance of unnecessary biopsies without missing significant PCa. It has also been shown to be a useful clinical marker in patients with a positive family history of PCa. Studies have suggested that these new diagnostic tests may be particularly useful in patients with a PSA range of 2.5-10 ng/ml. They have shown a slightly higher accuracy for PHI than for PCA3 with a further improvement in accuracy with their combination.^[14] However, further work is needed to confirm and generalize these conclusions to wider populations.

Novel Imaging

Raman spectroscopy is an optical technique that uses molecular specific scattering of light photons to interrogate biological material. When a sample is interrogated with laser light, most light is reflected back at the same wavelength. However, a small percentage of photons are scattered through interaction with the intramolecular bonds and exit the material at a different wavelength. Based on the link between disease and local molecular environment within cells and tissues, Raman spectroscopy has been investigated as a tool to characterize the molecular composition of tumor cells. It has been used to evaluate several malignancies, including those of the breast, colon, skin, lung, and cervix. However, adenocarcinoma of the prostate has been difficult to characterize accurately due to the histological heterogeneity of PCa. Raman molecular imaging (RMI) which combines digital imaging and analytical spectroscopy helps evaluate better the biochemical composition of interrogated material. In the setting of Gleason 7 disease (3 + 4), RMI distinguished the stroma and epithelium of Gleason pattern 3 and 4 regions in patients who progressed to metastatic disease and in those with no evidence of disease on a long-term follow-up.^[15] Further study to explore, develop, and validate a method using RMI for predicting disease progression in PCa is warranted.

Biopsy

The NCCN panel recommends considering biopsy in those aged 50-70 years with a positive DRE and/or serum PSA >3.0 ng/ml. However, the decision to perform biopsy should not be based on PSA values alone and should incorporate other important variables such as age, family history, PSA kinetics, health status, and patient preference.

Image-guided biopsy remains the mainstay for diagnosis of PCa. Transrectal ultrasound (TRUS) guided biopsy is done using an 18 gauge biopsy needle and specimens are taken from apex, mid-portion, and base to obtain two to three samples from each area. The presence of cancer, Gleason score, and percent of tissue sample occupied by cancer are considered. The Gleason histologic grading system is based on the extent of glandular differentiation and the pattern of growth of tumor in the prostatic stroma. It is the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1-5 with 5 being the most aggressive cytologically. The total score ranges between 2 and 10 with 10 being the most aggressive. Although the average number of biopsy cores taken at TRUS-guided prostate biopsy has increased overtime, this technique still has considerable limitations, including the blind nature of

sampling. Up to 25% of cancers might lie in the anterior prostate, outside of the standard TRUS-guided sampling zone, and so tumors in this area are more likely to be missed.

Disparity between biopsy findings and corresponding radical prostatectomy specimens is well-reported. Approximately, one in three cases of low volume, low risk disease are upgraded or upstaged on radical prostatectomy after initial standard TRUS biopsy.

There is considerable interest in the use of novel imaging, particularly in multiparametric MRI (mpMRI) to either select those who need a prostate biopsy, or guide needle placement during the procedure. Studies have shown that it reduces the detection of low risk PCa and the need for the biopsy, while improving the overall detection of intermediate/high risk PCa as compared to TRUS-guided biopsy.^[16] However, trials are still underway, and the NCCN panel does not recommend baseline imaging yet.

Staging

Primary tumor size (T), lymph node involvement (N), and presence or absence of metastasis (M), along with Gleason score and serum PSA have been used for staging. Based on this system developed by The American Joint Committee on Cancer, patients can be categorized into risk groups. Clinically localized PCa is characterized as the lower risk group which includes all of T1-T2a cancers. Among them, the very low risk group includes patients with Gleason score ≤ 6 , PSA density < 0.15 ng/ml/g, and < 3 positive prostate core biopsies with $< 50\%$ cancer in each core. The low risk group includes Gleason score < 7 and PSA < 10 ng/ml. Observation is recommended for such patients with life expectancy < 10 years. The high risk group includes any T3-4, Gleason > 7 , PSA > 20 , and intermediate risk includes the remainder^[17] [Figure 1].

Treatment

Treatment for PCa is highly individualized and depends on the severity of disease, functional status, age, and should be initiated after a detailed discussion about the various treatment options and side effects. Introduction of PSA has led to an increase in the number of cases diagnosed, dramatic down staging of PCa and diagnosis of localized tumors amenable to curative local treatment with either radiotherapy or surgery. Various treatment options include watchful waiting, active surveillance, prostatectomy, radiotherapy, hormone deprivation, and chemotherapy [Figure 2].

Active surveillance involves monitoring the course of disease and the prompt conversion to potentially

curative treatment if cancer progresses. It is preferred for low risk cancers and for patients with life expectancy ≤ 20 years. It includes PSA testing and DRE at least every 6-12 months with repeat biopsies annually or earlier, if they change significantly.^[18]

Radical prostatectomy

Radical prostatectomy is used for clinically localized PCa in patients with life expectancy ≥ 10 years. It involves the removal of the prostate, seminal vesicles, and pelvic lymph nodes and can be done by open or laparoscopic approach or with robotic assistance. PSA levels should be undetectable in 4-6 weeks after surgery. Levels > 0.2 mcg/L indicates recurrence and salvage radiotherapy to prostate bed is recommended.^[18] In a randomized trial done by Axelson *et al.* in men with early PCa, radical prostatectomy was associated with reduction in the rate of death from PCa, overall death and risk of metastases as compared to watchful waiting. Number needed to treat was 15 overall and 7 for men younger than 65 years. The study also concluded that men with extracapsular tumor growth had seven times higher risk of death and may benefit from local or systemic therapy.^[19]

Radiation therapy

Interstitial brachytherapy is used in patients with low risk cancer and delivers local high dose radiation to the prostate. In this procedure, small pellets of a radioisotope, iodine 125, or palladium 103 are implanted through the perineum under ultrasonographic guidance. Side effects include dysuria, hematuria, urinary urgency, frequency, urethral stricture, proctitis, and bladder cancer.^[10] External beam radiotherapy delivers radiation to the prostate from an external energy source. It is non-invasive and is effective for high risk cancer when combined with androgen deprivation. Pelvic lymph node irradiation with adjuvant/neoadjuvant androgen deprivation therapy (ADT) is recommended in intermediate (for 4-6 months) and high risk patients (for 2-3 years).^[18]

Androgen deprivation therapy

ADT is the first line therapy for advanced/metastatic PCa and recommended before, during, or after definitive radiotherapy for intermediate and high risk cancer.^[20] It can be achieved with bilateral orchiectomy, luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide or goserelin; or antiandrogens such as flutamide or bicalutamide. Antiandrogen therapy should precede or be given with LHRH agonists for at least 7 days in patients with overt metastasis as they can develop symptoms associated with testosterone flare with LHRH agonists alone.

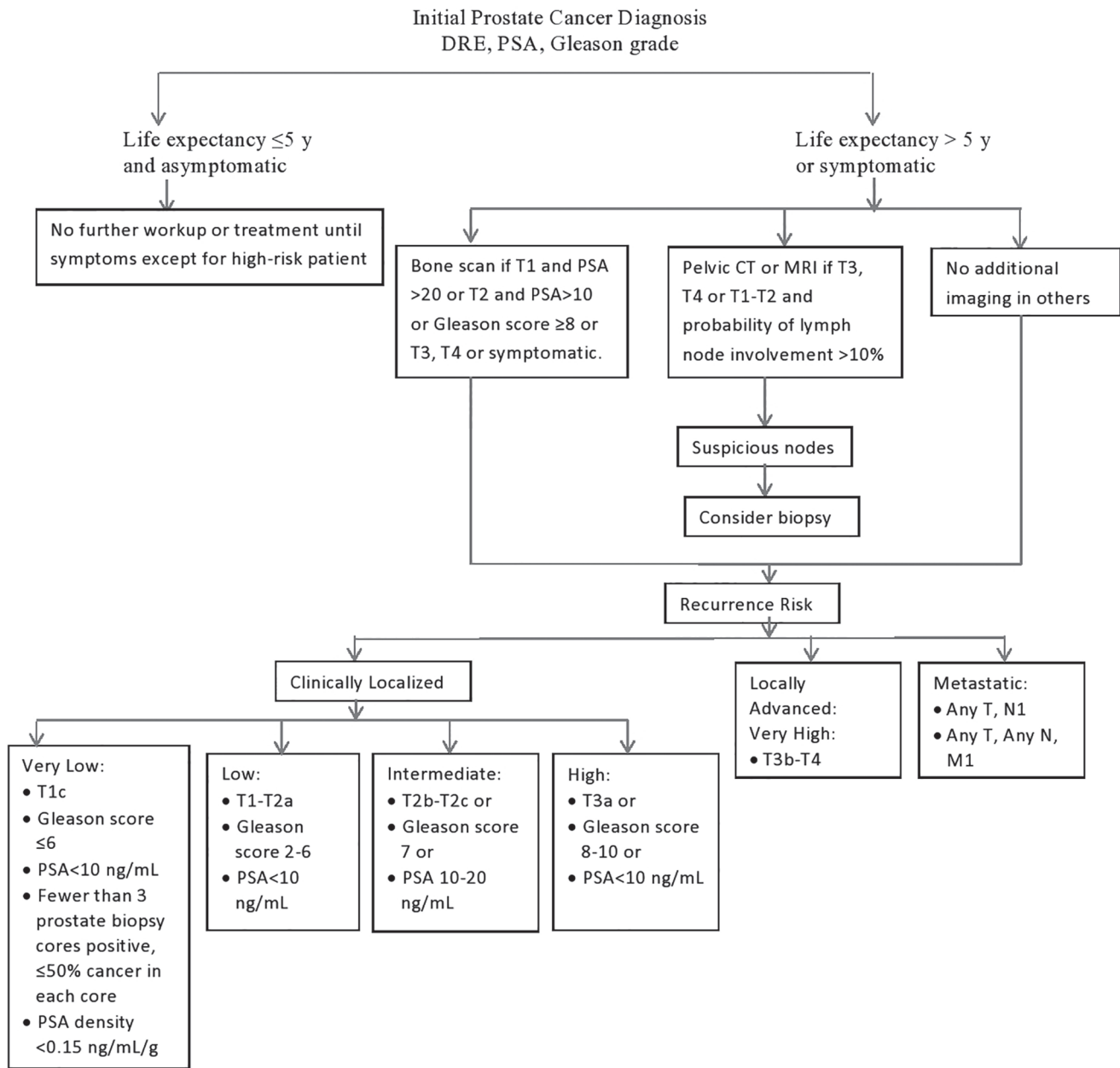


Figure 1: Prostate cancer staging and work up

Monotherapy with antiandrogens is less effective and not recommended.

In a meta-analysis done by Sasse *et al.*, androgen suppression with goserelin was found to have better overall survival and disease-free survival when compared to radiotherapy alone in patients at high risk of recurrence or metastases.^[21] Side effects include hot flashes, vasomotor instability, gynecomastia, decreased libido, erectile dysfunction, weight gain, and hyperlipidemia. Long-term effects are insulin resistance, diabetes mellitus, stroke, osteoporosis, and cardiac events.^[18,20] Baseline screening for underlying

osteoporosis is recommended prior to the initiation of ADT. Neoadjuvant LHRH agonist therapy for 3-6 months is recommended for men receiving radical radiotherapy for high risk disease and should be considered for men with intermediate risk disease. Adjuvant hormonal therapy for 2-3 years is recommended if they are at high risk of mortality.^[17] Immediate postoperative radiotherapy and adjuvant hormone therapy are not recommended after radical prostatectomy.^[17] Androgen deprivation is the mainstay of therapy for recurrent cancer but is not curative and the disease progresses to a state called castration resistant PCa (CRPC). Patients with castration refractory disease and who do not achieve

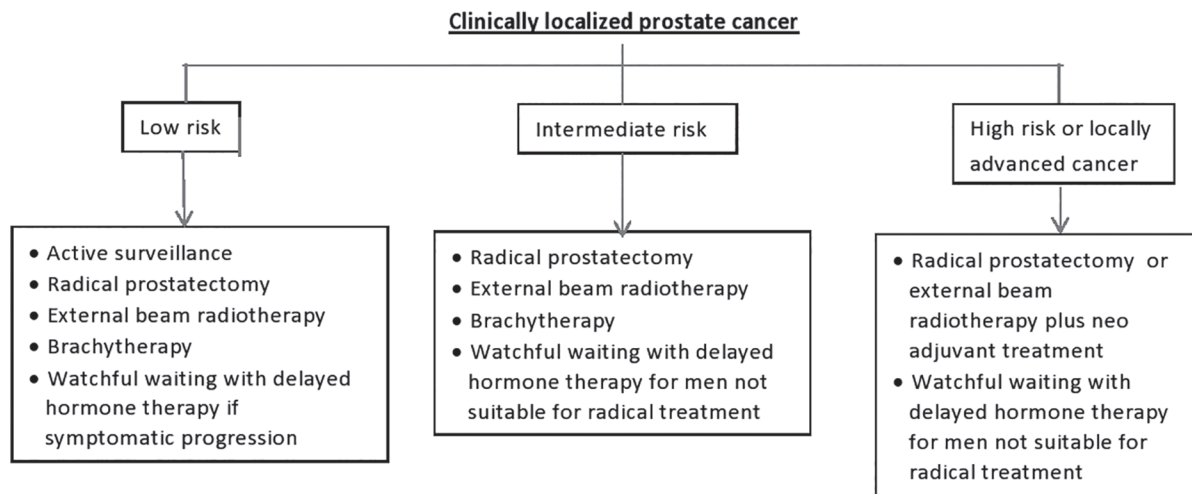


Figure 2: Treatment options for clinically localized prostate cancer

testosterone level <50 ng/dl should receive continued androgen suppression, can be considered for additional hormonal manipulations such as antiandrogens (second line), corticosteroids (third line), or estrogen or ketoconazole (fourth line) though the clinical benefit is not clear.^[17,18]

Chemotherapy

In men with metastatic hormone refractory PCa, docetaxel with prednisone was shown to have superior survival, serum PSA level, and quality of life than with mitoxantrone with prednisone.^[22] It is administered as 3 weekly schedules and is the first line of treatment. Cabazitaxel with prednisone is a second line in post docetaxel patients. Abiraterone acetate with prednisone is an option for patients who failed docetaxel. Sipuleucel T is an autologous prostatic acid phosphatase directed immunotherapy which has shown to improve survival in metastatic CRPC.^[23]

Skeletal related events (SRE) are a major cause of morbidity in PCa, especially in advanced cancer, metastatic CRPC, and osteoporosis associated with androgen deprivation. Despite osteoblastic appearance, there is a high osteoclastic activity which can be a target for treatment with bisphosphonates and denosumab.^[24] Renally dosed intravenous bisphosphonates such as zoledronic acid every 3-4 weeks is recommended. Denosumab given every 4 weeks subcutaneously was found to be better than zoledronic acid for the prevention of SRE in men with bone metastases from CRPC.^[25] Hypocalcemia is a common side effect of denosumab and patients may require supplementation with calcium and Vitamin D. Other options for painful bony metastasis include external beam radiotherapy with strontium-89 and samarium-153.^[18]

Conclusion

PCa is a complex disease with many controversial aspects of management. Several variables such as disease characteristics, life expectancy, and patient preference should be taken into account. Physicians should tailor screening and treatment to the individual patient to improve risk assessment, reduce overtreatment, and provide more selective therapy for patients with the high risk disease.

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Conflicts of interest

There are no conflicts of interest.

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