REVIEW ARTICLE

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Benign prostatic hyperplasia and prostate cancer: an overview for primary care physicians

Editor's Choice

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None.

SUMMARY

Benign prostatic hyperplasia (BPH) and prostate cancer (CaP) are major sources of morbidity in older men. Management of these disorders has evolved considerably in recent years. This article provides a focused overview of BPH and CaP management aimed at primary care physicians. Current literature pertaining to BPH and CaP is reviewed and discussed. The management of BPH has been influenced by the adoption of effective medical therapies; nonetheless, surgical intervention remains a valid option for many men. This can be accomplished with well-established standards such as transurethral resection of the prostate or with minimally invasive techniques. Prostate cancer screening remains controversial despite the recent publication of two large clinical trials. Not all prostate cancers necessarily need to be treated. Robot-assisted prostatectomy is a new and increasingly utilised technique for CaP management, although open radical retropubic prostatectomy is the oncological reference standard. The ageing of the population of the developed world means that primary care physicians will see an increasing number of men with BPH and CaP. Close collaboration between primary care physicians and urologists offers the key to successful management of these disorders.

Review Criteria

- PubMed-indexed English language articles pertaining to BPH and prostate cancer
- Clinical experience and judgment of the senior author (MJN)

Message for the Clinic

Benign prostatic hyperplasia and prostate cancer are common problems for ageing men. Management of both conditions is technologically driven and undergoing significant change.

Introduction

Prostatic disease causes considerable morbidity in ageing men. Benign prostatic hyperplasia (BPH) can lead to bothersome lower urinary tract symptoms (LUTS) and/or to acute urinary retention (AUR). Recent decades have seen an expansion of the role of medical therapy for BPH as well as the emergence of new technologies for surgical management.

Prostate cancer is common and early detection may be beneficial; however, mass screening has become controversial. Not all prostate cancers may need immediate treatment. For some men, watchful waiting or active surveillance are options. The introduction of robot-assisted surgery for prostate cancer is an important new technology.

This review provides an overview of developments in BPH and prostate cancer. As baby boomers age, physicians will see an increasing number of men with these problems.

Benign prostatic hyperplasia

Benign prostatic hyperplasia is the fourth most common diagnosis in older men (1). More than 50% of men over age 50 years are affected; by the age of 80 years, 90% of men will have an enlarged prostate. Progression to urinary retention may occur, with an accompanying risk of recurrent urinary tract infections, bladder calculi and occasionally renal insufficiency. Management options for BPH include medications, minimally invasive therapies and prostate surgery.

The most common presentation of men with BPH is bothersome LUTS such as frequent urination, urgency to urinate, nocturia, weak urinary stream, incomplete bladder emptying, straining to void and an intermittent stream. A patient may have multiple symptoms, but be bothered primarily by one of them. Prostate cancer, bladder cancer, urinary tract infections, prostatitis, urethral stricture and bladder stones can also cause LUTS.

To a large extent, malignant disease can be ruled out by performing a digital rectal examination (DRE), a prostate-specific antigen (PSA) blood test and a urinalysis. If these investigations are all normal, BPH is the most likely cause of the patient's LUTS for men over 50 years. Elevated PSA and/or a nodular prostate can be indicative of prostate cancer. Microscopic haematuria with urinary symptoms can be indicative of bladder cancer or prostate cancer.

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Evaluation of bothersome LUTS, especially those characterised by sensation of incomplete emptying or double voiding (urinating twice within 10–15 min) with the second void containing 30% or more of the first void volume, can include a postvoid residual (PVR) determination. A PVR greater than 300 ml may suggest a higher risk of urinary retention requiring surgical therapy for BPH (2). Despite the absence of a universally accepted 'normal' value for PVR, data exist suggesting that elevated PVR [over 39 ml in the Medical Treatment of Prostatic Symptoms (MTOPS) study and over 93 ml in the Alfuzosin Long Term Efficacy and Safety Study (ALTESS)] may portend worsening of patient-reported International Prostate Symptom Scores (IPSS) over a 4-year period (3). Furthermore, the MTOPS study demonstrated increasing PVR as a predictor of AUR (4). It should be noted that measurement of PVR can be deferred in favour of an empirical trial of medical management (5) in patients whose LUTS are suggestive of BPH. Failure of LUTS to improve with an empirical trial of medications can be further evaluated by PVR determination and/or referral to a urologist.

The risk for BPH progression increases as a man's prostate size increases. Results from the MTOPS trial (4) and the PLESS trial (6) demonstrated an increased risk of urinary retention and prostate surgery in men with enlarged prostate glands. A population-based study from Olmsted County, MN reported a 2% reduction per year in urinary flow rates and an increase in prostate volume of 1.6% per year (7). Estimation of prostate size in the primary care setting poses some challenges. However, PSA can be used as a surrogate measure of prostate size; a value of 1.5 ng/ml correlates to a prostate volume of 30 g, which can in turn be regarded as enlarged (8).

Medications are generally first-line treatment for men who present with LUTS from BPH. There are two types of medications available; alpha blockers and 5-alpha-reductase inhibitors. LUTS from BPH can be caused by increased smooth muscle tone in the bladder neck and prostatic urethra and/or increased prostate size and resulting blockage of the bladder outlet. Alpha blockers relax smooth muscle tone during urination and effectively increase the size of the prostatic lumen to facilitate urination. Alpha blockers tend to work quickly, usually within a matter of a few days. 5-alpha-reductase inhibitors shrink the hyperplastic tissue in the prostate by blocking the conversion of testosterone to dihydrotestosterone, the major prostatic androgen. This tissue shrinkage reduces bladder outlet obstruction. The 5-alpha-reductase inhibitors work more slowly than alpha blockers and can take 6–12 months to relieve urinary symptoms.

Studies have shown that alpha blockers do not alter the risk of urinary retention or the need for prostate surgery, but 5-alpha-reductase inhibitors significantly decrease the risk of these two complications in men with enlarged glands (7,9). In a recent trial in men with enlarged prostates ≥ 30 ml, the 5-alpha-reductase inhibitor dutasteride gave superior symptom improvement when compared with the alpha blocker tamsulosin. In this 4-year trial, the combination of tamsulosin and dutasteride together gave superior symptom improvement when compared with either monotherapy arm alone (10). Analogous results have been obtained in the MTOPS study, which employed a combination of doxazosin and finasteride (11).

Side effects of alpha blocker therapy include postural hypotension with less selective drugs such as terazosin and doxazosin. This problem can be addressed by slow dose escalation and bedtime dosing. Subjective dizziness, rather than overt hypotension, is uncommonly reported with more selective alpha blockers such as tamsulosin or alfuzosin. In addition, alpha blockers will sometimes cause retrograde ejaculation. 5-alpha-reductase inhibitors are generally well tolerated, but may cause problems with libido for some men. (12)

Some men do not respond adequately to medical management for their urinary symptoms, some have undesirable medication side effects and others do not want to take chronic medications. In these men, surgical options for treatment can be considered. Minimally invasive options include thermotherapy using transurethral needle ablation (TUNA) or transurethral microwave therapy (TUMT). These treatment options carry the advantage of minimal long-term side effect risk and significant improvement in urinary symptoms in properly chosen patients.

The other surgical option is transurethral resection (TURP) or laser treatment of the prostate (13,14). TURP is regarded as the historical gold standard for endoscopic management of the enlarged prostate; however, comorbidities such as bleeding and TUR syndrome (hypervolemic hyponatremia related to absorption of large volumes of irrigant) have prompted interest in alternative modes of prostate ablation. A variety of lasers have been used to deliver energy to the prostate. Holmium laser enucleation of the prostate (HoLEP) recapitulates the excision of the BPH adenoma, which is achieved by open simple prostatectomy. Indeed, high-level evidence exists, supporting equivalent outcomes for HoLEP as compared with TURP (15) However, HoLEP is regarded as a challenging procedure to learn and therefore may be somewhat slower to be adopted by the urologic community (15).

A parallel development in laser technology has been photoselective vaporisation of the prostate (PVP). A 532-nm laser produces energy selectively absorbed by haemoglobin, leading to vaporisation of prostatic tissue with an underlying zone of coagulation (15,16). This vaporizing action may translate to superior haemostasis, and PVP has been advocated for treatment of patients on anticoagulant or antiplatelet therapy (16). Long-term effectiveness (> 5 years) of laser treatment modalities is yet to be established. All prostate ablative techniques carry the risk of retrograde ejaculation (50–90%) and urinary incontinence (about 1%). Erectile dysfunction is uncommonly reported after TURP; similarly, evidence exists showing no statistically significant change in erectile function after PVP as measured by the Sexual Health Inventory in Men (SHIM) score (13,14,17).

Prostate cancer

Prostate cancer (CaP) is the most common non-cutaneous cancer in American men (18). It is a malignancy with a broad range of biological potential; one challenge for physicians is to identify and cure aggressive cancers while not over-treating indolent tumours (19). Population-based screening has been proposed as a means of reducing CaP-specific morbidity and mortality.

Produced exclusively by prostatic epithelial cells, PSA is a serine protease with a role in semen liquefaction (20) and it may have other functions in reproduction (21). Starting in the late 1980s, serum PSA determinations gained prominence as a means of screening for CaP. Consequently, a stage migration occurred such that most newly diagnosed prostate cancers are confined to the prostate (20,22).

Many physicians regard 4.0 ng/ml as the upper limit of normal for serum PSA (20). However, evidence supports interpretation of PSA in a way that is more tailored to individual patients. The Prostate Cancer Prevention Trial (23) showed that among 2,950 men with PSA less than 4.0 ng/ml, there was a 15.2% prevalence of CaP. Of the prostate cancers detected, there was a 14.9% incidence of Gleason sum 7 or higher tumours, which pose a significant risk of cancer progression. Physicians should therefore be cautious about using the 4.0 ng/ml cutoff for all patients.

Prostate-specific antigen levels typically increase with age (Table 1). An analysis by Oesterling et al. (24) led to the establishment of age-specific reference ranges for PSA, which may help improve the cancer detection rate in younger men (who are more likely to derive a survival benefit from treatment of CaP) while reducing the rate of unnecessary biopsy in older men. Furthermore, African-American men may normally have higher PSA levels than other groups and race-specific PSA values have been developed (18). PSA velocity (PSAV) has been proposed as an adjunct to conventional screening. One group (25) proposes that a PSAV > 0.35 ng/ml/year in men under 60 years may be an indication for biopsy when derived from at least three PSA determinations separated from each other by at least 3 months and spaced out over at least 18–24 months. A PSAV of > 0.75 ng/ml/year is used for men over 60 years. PSAV has the added advantage of potentially being more likely to diagnose aggressive CaP (26).

Table 1 Age-specific PSA reference ranges (reference 14)

Age Range (years)	PSA Reference Range (ng/ml)
40–49	0.0–2.5
50–59	0.0–3.5
60–69	0.0–4.5
70–79	0.0–6.5

PSA, prostate-specific antigen.

Most circulating PSA is bound to serum proteins; this binding is contingent on proteolytic processing of naïve PSA, which, for yet to be completely clarified reasons, is reduced in CaP. Therefore, patients with CaP may have a reduced percentage of free PSA (fPSA) in circulation (27). A free PSA over 25% in a patient with a total PSA between 4 and 10 ng/ml implies an 8% risk of harbouring CaP; on the other hand, a free PSA less than 10% in such a patient suggests a 56% risk of CaP (27,28). Furthermore, lower percentages of free PSA suggest a higher likelihood of adverse prognostic features for the radical prostatectomy specimen (28).In general, free PSA is most helpful in determining the need for repeat biopsy after a negative initial biopsy; as such, it is most likely to be useful to urologists rather than as an adjunct to total PSA in the hands of primary care physicians.

Several factors can alter serum PSA determinations. Treatment with 5-alpha-reductase inhibitors such as finasteride and dutasteride decrease serum PSA by about 50% within 12 months of starting treatment (29). Serum PSA determinations also can be skewed by conditions such as urinary tract infections, urethral catheterisation and transurethral endoscopic procedures. Ejaculation can significantly increase PSA in some men, although not all investigators agree on this point (30). This possibility can

be managed by asking men to refrain from ejaculation for 24–36 h before the PSA test. Maximally effective screening for CaP combines PSA and DRE. One study suggested that screening with PSA alone misses 17% of prostate cancers when a biopsy cutoff of 4.0 ng/ml is employed (31).

Initial results from two trials addressing the benefit of screening for CaP have recently been published. The Prostate, Lung, Colorectal and Ovarian (PLCO) trial randomised 76,693 men to PSA screening or control groups (32). The trial failed to find a difference in CaP-specific mortality at 7–10 years. Limitations included high utilisation of screening by patients in the control arm, producing more diagnoses of prostate cancer in purportedly unscreened patients. In addition, there is a 'lead time' of at least 10 years between diagnosis by screening and the emergence of clinically detectable manifestations of CaP (33). Thus, 7–10 year follow up may be insufficient to detect a mortality difference.

On the other hand, the European Randomized Study of Screening for Prostate Cancer (ERSPC) randomised 182,160 patients (34). Using a biopsy PSA cutoff of 3.0 ng/ml, the investigators found a 20% reduction in the CaP death rate for the screened group. To save one life required screening 1,410 men and treating 48 for CaP. This implies a substantial level of over-diagnosis, which may have been exacerbated by a relatively low biopsy PSA cutoff. The median follow-up in the initial report was 9 years. Like PLCO's results, those obtained by ERSPC are the product of relatively short follow up.

Screening for CaP exposes patients to risks, including rare but potentially serious complications of biopsy (35) or the well defined morbidities of prostate cancer treatment. Absent an unequivocal survival benefit from population-based screening, guidelines promulgated by the U.S. Preventive Services Task Force stop well short of recommending screening and explicitly recommend against PSA screening for men over 75 years(36). In the end, the decision to screen for prostate cancer rests with the patient. Taking into account attributes such as age, race, family history and PSA kinetics, primary physicians can provide appropriate counselling regarding PSA screening. The American Urological Association (AUA) in its 2009 Best Practice Statement (37) avoids setting explicit PSA thresholds for biopsy and emphasises the need for informed consent from the patient in undergoing PSA screening.

The challenge of CaP management is to decide who needs treatment and when. Cancer grade as revealed on biopsy can be informative. Unfortunately, the sampling error inherent in needle biopsy means that there is an appreciable risk of under-grading the tumour because an area of higher grade disease was missed. Various protocols exist for identifying low-risk CaP (38) and some such patients may be offered active surveillance (39). To mitigate the danger of under-grading, these patients typically undergo repeated prostate biopsies at predetermined intervals, and PSA levels and DRE findings are monitored. If progression of disease (increased PSA, PSAV, or discovery of higher grade or bulkier cancer on biopsy) occurs, definitive therapy is offered.

Active surveillance differs from watchful waiting, in which men with limited life expectancy or severe comorbid disease are monitored for the emergence of problematic local extension or metastatic disease before palliative therapy is instituted. Specifically, active surveillance includes repeat prostate biopsies and close PSA follow up and patients need to recognise the risk of needing definitive therapy as well as the potential for development of incurable CaP. As experience with active surveillance is accrued, its acceptance by patients and physicians will likely increase. Indeed, the NICE guidelines issued by the UK's National Health Service explicitly recommend active surveillance as a first-line option for men with low-risk CaP (40). Appropriately selected patients do not experience undue anxiety or distress during active surveillance (41).

Localised CaP can be treated with surgery or radiation therapy. Spurred by improved understanding of surgical anatomy (42), radical retropubic prostatectomy (RRP) has excellent oncological outcomes. In experienced hands, incontinence occurs in fewer than 10% of patients and potency is preserved in 50–60% of patients, although men with any degree of preoperative erectile dysfunction (ED) are predetermined to fare worse from a potency standpoint even if they are preoperatively responsive to erectogenic medications. (43). Robot-assisted laparoscopic radical prostatectomy (RALRP) accounts for a steadily increasing proportion of prostate cancer operations in this country, although long-term oncological outcomes remain undefined (43). Moreover, no prospectively acquired, randomised evidence suggests superior potency or continence outcomes for RALRP (44).

Radiation therapy for prostate cancer has become more effective and better tolerated as techniques for increasing the radiation delivered and excluding bladder and bowel from treatment fields have evolved. Nonetheless, rectal or bladder toxicity manifesting as haematochezia, haematuria, or irritative LUTS are recognised sequelae. Concerns have been raised about second malignancies in patients treated with radiation for prostate cancer (45) In some high-risk patients, outcomes may be improved by combin-

ing radiation therapy with androgen ablation (46). Prostatic brachytherapy is another method of delivering radiation therapy. It is associated with significant short- to mid-term voiding symptoms and may not be feasible in patients with larger glands (47). Moreover, brachytherapy in combination with external beam radiation may offer enhanced freedom from biochemically detectable disease in the setting of high-risk prostate cancer (48).

Emerging definitive therapies for prostate cancer include high intensity focused ultrasound (HIFU) and cryotherapy (49,50). HIFU involves imaging the prostate with transrectal ultrasound and delivering ultrasound energy to produce tissue heating and cavitation. The technique has been in use in Europe with mixed short-term results (51,52). Despite a biochemical complete response rate of only 92% in one series (52), interest in HIFU remains strong because of its minimally invasive nature. Cryotherapy delivered by a transperineal route under Transrectal ultrasound (TRUS) guidance has been described for both primary and salvage treatment of CaP. Technical improvements in available equipment are expected to reduce the incidence of local complications such as urethral fistulas and 94% disease specific survival has been reported at 5 years (53). However, the incidence of ED after cryotherapy is appreciably higher than after nerve sparing prostatectomy or brachytherapy (54,55).

As Huggins first observed regression of prostate cancer after orchidectomy (56), the role of androgens in CaP has been exploited for therapeutic ends. Androgen ablation by orchiectomy, androgen antagonists such as bicalutamide and/or Luteinizing hormone release hormone (LHRH) analogues such as leuprolide is the mainstay of treatment for metastatic CaP. Given enough time under androgen ablation, CaP will generally become castration-resistant and pose a risk of progression. Mechanisms for this escape from suppression include constitutive activation of the androgen receptor (AR), inappropriate expression of downstream targets of the activated AR, or intratumoural steroidogenesis via a CYP17-dependent mechanism (57).

It has been observed that the guiding principle of cancer treatment should be *primum succerere*: first hasten to help (58). The challenge in prostate cancer treatment is to help those men who need it, striving to minimise the morbidity of treatment through judicious selection of the modality and timing of treatment.

Benign prostatic hyperplasia and prostate cancer are diseases that will increase in prevalence as the population ages. Medical management has emerged as a good strategy for many men with BPH, although advancing technology has changed the face of prostatic surgery for those men who are unsuccessful with medical management or who prefer intervention. PSA screening has changed prostate cancer management and arguably made definitive local therapy with surgery or radiation a possibility for many more men. However, the question remains of who needs treatment and when.

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