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A Primary Care Approach to Managing Localized Prostate Cancer

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Editor's Note—*Prostate cancer is the most commonly diagnosed cancer among men in the United States. While few men initially present with symptoms of this disease, many patients will develop symptoms that may require treatment such as bone pain, hematuria, and urinary obstruction, and 10-20% will eventually succumb. Thus, prostate cancer is a significant clinical entity in any primary care practice.*

Carcinoma of the prostate has been a source of confusion and controversy for years. Its heterogeneity of presentation and variability in clinical behavior make it one of the most controversial health care topics of the 21st century. The development of prostate specific antigen (PSA) in the 1980s and FDA approval for its clinical use in 1991 led to much debate as to who should be screened, at what age, and how they should be screened. With the recent diagnoses of such high-profile cases as New York City Mayor Rudy Guliani and New York Yankees' manager Joe Torre, prostate cancer has become a common household topic. American men are beginning to take active roles in their own health care and are searching for increased personal knowledge of common health problems. Physicians must have adequate knowledge regarding appropriate prostate cancer screening and management in order to assist patients with decision making.

Once prostate cancer is diagnosed, the clinical course can vary greatly. This disease has a unique spectrum of biological activity ranging from indolent and inconsequential illness to virulent disease and subsequent death. The broad spectrum of clinical behavior makes treatment decisions difficult for patients and physicians alike.

This article will review the epidemiology of prostate cancer, its etiology, and pathogenesis, including age, hormonal influences, genetic predisposition, diet, and environmental factors. The controversial topic of screening will be addressed including the effect of screening, methods of screening, and the appropriate screening population. Transrectal ultrasound-directed prostate biopsy, pathology, and staging of prostate cancer will be reviewed. The final topic of discussion will be the management of localized disease, including watchful waiting, surgical extirpation, radiation therapy, cryotherapy, androgen deprivation, and treatments of the future.

Epidemiology

Prostate cancer is the most common malignancy in American men. This year, in the United States alone, it is expected that more than 198,100 new cases of prostate cancer will be diagnosed.[2] Prostate cancer is the second most common cause of cancer-related death, with about 40,000 men dying annually. The ratio of approximately 5 newly diagnosed cases for every 1 death from cancer each year has remained relatively constant over the past 30 years. Prostate cancer is a disease of aging and rarely presents in men younger than age 40. The incidence increases progressively until it reaches a peak in the

8th decade. While prostate cancer is unequivocally lethal in some patients, most men die *with* their disease rather than *of* their cancer. Autopsy studies have demonstrated that histologically apparent prostate cancer can be found in approximately 42% of men older than 50 years of age who die of other causes. The lifetime risk that an American man will be diagnosed with prostate cancer is estimated to be 11%, while the actual risk of dying from this disease is only 3.6%.[1-3]

Etiology and Pathogenesis

Several factors have been suggested as etiologic antecedents to prostate cancer. These include age, hormonal influences, genetic predisposition, diet, and environmental factors. It is indisputable that the incidence of prostate cancer increases with age. The probability of developing clinical prostate cancer is less that 1 in 10,000 for men younger than 40 years of age, 1 in 103 for men aged 40-59 years, and 1 in 8 for men 60-79 years.[4] Prostate cancer incidence increases faster with age than does any other major cancer.

The prostate is an androgen-dependent organ. Therefore, testosterone is required for normal prostatic epithelial growth as well as the development of both benign prostatic hyperplasia (BPH) and prostate cancer.[5] In the rare instance in which men have been castrated prior to puberty, prostate cancer is nonexistent. The majority of cancer cells grow and thrive in the presence of male hormones and castration usually produces dramatic regression of cancer.[6]

Genetic predisposition confers a higher risk of prostate cancer and may be second only to age as the most important risk factor for disease. Several studies have reported a higher incidence of prostate cancer among primary relatives (father or brother) of prostate cancer patients.[7] Familial and hereditary forms of prostate cancer have been identified.[8,9] Both are associated with early onset of disease. They form a significant proportion of prostate cancers occurring in men younger than 55 years of age. However, they constitute only 9% of all prostate cancer diagnoses. There is a wide variation in prostate cancer incidence among different ethnic groups. Asian men—not just in their countries of origin but in the United States as well—have a relatively low incidence of prostate cancer, while African American men have the highest incidence of prostate cancer in the world.[10,11] The Surveillance, Epidemiology, and End Results (SEER) program database demonstrated a 30% greater incidence of prostate cancer among African American men compared to Caucasian American men.[12] The 5-year survival rates for all stages of prostate cancer are 62% for African American men and 72% for Caucasian American men.[13]

The importance of dietary and environmental factors is demonstrated by the fact that Japanese men living in their native country have a relatively low incidence of prostate cancer; however, when they move to the United States, their prostate cancer risk increases dramatically.[14] Dietary fat has been linked to prostate cancer in several studies.[15] Animal models with prostate tumors have shown that in the presence of a high-fat diet (controlled for caloric intake), tumors grow more quickly.[16] Other authors have also found that body mass index is highly correlated with the risk of prostate cancer.[17,18]

Screening

Because prostate cancer is usually asymptomatic until late stages, early detection is of critical importance. For more than a century previously, prostate cancer screening consisted only of digital rectal examination (DRE). Normally, the prostate gland consistency is similar to that of the thenar eminence. It is rubbery and has mobility with palpation. The gland with BPH may have a spongy or indurated consistency, while the gland with palpable prostate cancer may have stone-hard nodules and may be fixed in position due to local extension through the capsule and/or into the seminal vesicles. Today, most diagnosed prostate cancers are not palpable on DRE. The positive predictive value for DRE in current studies ranges from 21% to 53%, depending on the degree of suspicion for cancer and whether the population studied is referred or screened. DRE alone has only fair reproducibility in the hands of experienced examiners. It misses a substantial proportion of nonpalpable cancers and detects those that are more likely to be at an advanced stage. The discovery of PSA and highly sensitive serum assays in the 1980s led to dramatic changes in the way prostate cancer is diagnosed and treated. PSA is a serine protease, which is produced by the prostatic epithelium and periurethral glands. Normally, it is found in low concentrations in serum (0.0-3.99 ng/mL).[22] The presence of prostatic diseases, including prostate cancer, BPH, and prostatitis, are the most important factors affecting serum levels of PSA. Initially, it was thought that PSA would not be helpful in prostate cancer detection because of the overlap in serum levels between men with BPH and those with cancer. However, numerous studies have document-

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ed the validity of PSA as a method for assessing the presence of prostate cancer.[23-27]

Impact of Screening. Currently, prostate cancer screening, consisting of a DRE along with a serum PSA, is practiced by the vast majority of urologists[28] as well as a large proportion of primary care practitioners.[29] Despite this trend, the entire subject of prostate cancer screening has sparked much controversy and debate. Questions such as who should be screened, at what age, how they should be screened, and whether anyone should be screened at all, have been at the forefront of this controversy. In the early 1990s, the detection of prostate cancer rose significantly. This coincided with the development of PSA-based screening. Studies from Olmsted County, Minnesota, demonstrated a 3.4-fold increase in detection of prostate cancer between 1983 and 1992.[30] Likewise, data from the SEER program showed an 80% increase between 1986 and 1991.[31] The introduction of any effective screening program should result in an increased detection of disease. However, if screening detects clinically relevant cases, then incidence rates eventually return to near prescreening levels. This is the "cull effect."[32] Studies have shown that the detection of prostate cancer has been declining since 1992 and are now preaching the incidence rates of the pre-PSA era.[33]

Several questions arise as a result of these data. Are we detecting cancers that would not have become clinically evident, thus subjecting patients to unnecessary therapies? The proportion of low-grade tumors at the time of diagnosis increased modestly prior to 1992 and has been steadily declining since then, while the detection of moderately differentiated cancers has been steadily increasing since the 1980s. Today nearly 70-80% of men have pathologically organ-confined cancer at diagnosis compared to only 20-30% in the pre-PSA era.[34] The fact that the US death rate from prostate cancer has decreased in the last 5 years (during the PSA screening era) is strong inferential evidence that earlier diagnosis by screening and, thus, earlier treatment does lead to improved survival.[35] Definitive proof awaits completion of long-term clinical trials currently in progress.

Screening Initiation and Optimal PSA Cut-Points. The most effective method for early detection of prostate cancer is the combined use of DRE and PSA. The American Cancer Society and the American Urological Association currently recommend DRE and PSA testing annually beginning at age 50. African American men and those with a family history of the disease should consider initiating screening earlier at the age of 40. Although 4.0 ng/mL has traditionally been used as the upper limit of normal for PSA testing, 20% of men with diagnosed prostate cancer have a PSA level less than 4.0 ng/mL.[36] Oesterling and associates established age-specific reference ranges for PSA in an attempt to improve sensitivity of cancer detection in younger men and enhance specificity in older men (*see Table 1*).[37] This idea was predicated on the observation that PSA is higher in older men regardless of whether they have cancer. While most urologists agree that 2.5 ng/mL is an appropriate cut-point for younger men in whom early prostate cancer detection and aggressive treatment would be most beneficial, raising PSA cut-points to greater than 4.0 ng/mL for older men has led to some disagreement. Studies have shown that for any given PSA level between 4.0 and 10.0 ng/mL, older men are more likely to have clinically detectable prostate cancer.[38] Furthermore, a prospective clinical trial recently demonstrated that raising the PSA cutoff from 4.0 to 4.5 ng/mL among men 60-69 years of age would result in missing 8% of organ-confined cancers, and raising the PSA cut-point to 6.5 ng/mL among men older than the age of 70 missed 47% of cancers.[39] Currently, age-specific PSA range is used in combination with other screening strategies and is not used as an isolated screening test.

Table 1. Age Adjustments for PSA

Age Range	Range of Normal PSA
40-49	0-2.5 ng/mL
50-59	0-3.5 ng/mL
60-69	0-4.5 ng/mL
70-79	0-6.5 ng/mL

Free PSA. The majority of PSA in serum is bound to protease inhibitors with only a minority existing in the unbound form.[40] For unknown reasons, the proportion of PSA that is unbound (percent-free PSA) is lower in men with prostate cancer than in men with benign prostates.[41] PSA specificity for detecting prostate cancer has improved for total PSA levels in the range of 4.0-10.0 ng/mL by the addition of free PSA. When total PSA is less than 4.0 ng/mL, free PSA testing is unnecessary. However, when PSA levels range from 4.0 to 10.0 ng/mL, free PSA provides independent predictive information about the presence or absence of cancer above that provided by other clinical indices such as age, total PSA, DRE, and prostate size. Currently, there is no set protocol as to when and how free PSA should be used.[42] The single optimal cut-point for free PSA remains elusive. For most men, a cut-point of 25% is reasonable. Men who have a percent-free PSA greater than 25 have an 8% chance of having prostate cancer, while those with a percent-free PSA of 10 or less have a 58% chance of having cancer.[43] In general, percent-free PSA helps clinicians determine whether to recommend further evaluation including prostate biopsy in men with a serum PSA between 4.0 and 10.0.

Complexed PSA. The proportion of PSA bound to protease inhibitors can be measured by a complexed PSA assay. Although this screening test is not yet in routine clinical use, recent studies that led to FDA approval of the test have shown that complexed PSA has a specificity higher than that of total PSA and similar to percent-free PSA. Furthermore, it can be used as a single test.[44] Future studies will determine the clinical value of this screening tool.

PSA Velocity. The PSA velocity refers to the rate of change in PSA level over time. The rationale behind this calculated measurement is that men with clinically significant prostate cancer experience more rapid rises in PSA compared to men without disease. This concept was discovered during analysis of archived serum from the Baltimore Longitudinal Study of Aging.[45] In this study, it was determined that an increase in PSA greater that 0.75 ng/mL/y is a reasonable cutoff above

which prostate cancer should be suspected. PSA velocity is most helpful in patients who are on long-term surveillance for the possible development of prostate cancer; and in those with known prostate cancer being managed by watchful waiting to predict possible progression on serial studies.

PSA Density. It is well recognized that BPH can result in PSA elevation in the absence of cancer.[46] Therefore, the volume of normal prostate tissue is directly proportional to serum PSA. In an attempt to control for prostate size, the concept of PSA density was developed. PSA density is the total PSA divided by prostate volume as determined by transrectal ultrasound. A number of authors have suggested the use of PSA density to determine the patient who merits a prostate biopsy. It has been suggested that an optimal cutoff is 0.15 ng/mL.[2,47,48] Any calculated value greater than this is an indication for biopsy; however, PSA density should not be the sole criterion for biopsy.

Transrectal Ultrasound-Directed Prostate Biopsy

The diagnosis of prostate cancer in a man at high risk for the disease (eg, elevated PSA, abnormal DRE) is obtained with a transrectal prostate biopsy. Transrectal ultrasound (TRUS) is performed as an outpatient, typically without sedation in the lithotomy position. Because biopsy needles are passed through the rectum, broad-spectrum antibiotic coverage is given immediately prior to the biopsy and for 24-72 hours. A patient on Coumadin must discontinue its use prior to undergoing biopsy. In general, complications include rectal or urinary hemorrhage, or urinary tract infection with possible sepsis. Neither complication is likely when appropriate patients are chosen and antibiotic prophylaxis is used. TRUS alone is not an accurate method for localizing early cancer and, thus, is not recommended as a screening tool. While prostate cancer may appear hypoechoic on TRUS images, it may also be hyperechoic or even isoechoic and nonmalignant lesions can appear similar; hence, no absolute ultrasound criteria exist. The major role of TRUS, therefore, is to guide accurate placement of the biopsy needles to ensure representative sampling of prostate tissue. Hodge and associates were the first to suggest that sextant biopsies of the prostate (apex, mid-gland, and base from each side of the gland) resulted in optimal prostate cancer detection.[49] More recently, Ravery and colleagues have increased the number of cores obtained at biopsy from 6 to 10, with a resultant increase in cancer detection of 18.5%.[50] Levine and colleagues performed sextant biopsies in a group of 137 men followed by immediate repeat sextant biopsies.[51] Prostate cancer was diagnosed in 31% of patients, with 21% diagnosed in the first set and an additional 10% with the second set of biopsies. These data suggest that sextant biopsies are probably inadequate for all but the very smallest of prostate glands. The exact optimum number of cores remains unknown and is a balance of the risk of missing cancer and patient discomfort. Contemporary clinical experience suggests that patients are probably best served with 8-12 cores.

Pathology and Staging

Prostate cancers are almost exclusively adenocarcinomas, which arise from prostatic acinar cells. Seventy percent of prostate cancers arise in the peripheral zone (true prostate that does not include the periurethral glands or transition zone where BPH arises), 15-20% arise in the central zone, and 10-15% arise in the transition zone. There are several systems of grading prostate cancer based on the degree of glandular differentiation, cytologic atypia, and nuclear abnormalities. The most widely used system is the Gleason grading system, which assigns 2 grades to each area of prostate cancer based on a major and minor pattern of glandular differentiation (*see Table 2*).[52] Gleason sums 2-4 represent well-differentiated cancer, 5 - 6 moderately differentiated, and 7-10 poorly differentiated. Tumor grade is one of the most clinically useful predictors of prostate cancer progression.

Clinical staging is based on the results of DRE and PSA. Currently, the Tumor-Node-Metastasis (TNM) classification is the most widely used system for staging prostate cancer (*see Table 3*).[53] The goals of staging are 2-fold: to evaluate prognosis and to direct therapy based on the extent of disease. Fortunately, fewer than 5% of men with newly diagnosed prostate cancer have metastatic disease at the time of diagnosis.[2] Therefore, one must be judicious in the use of tests to assess for the presence of metastases. Generally, men with well, or moderate degrees of differentiation (Gleason sum 2-6) and PSA values less than 10 ng/mL have an extremely low risk of metastases and, therefore, don't require routine imaging with CT, MRI, or bone scans. If the PSA is 10 ng/mL or greater or if the Gleason score is 7 or greater, then an isotope bone scan is recommended to evaluate for the presence of bone metastases. In addition, if the patient has clinical T3 disease (tumor palpable outside the prostate), a pelvic CT or MRI may be useful to evaluate for pelvic lymphadenopathy.

Management of Prostate Cancer

Decision making about appropriate management of prostate cancer is filled with controversy and must be based on the patient's age and general health, life expectancy, the clinical stage and histologic grade of tumor, quality of life, available resources, and patient preferences. Figure 1 is a suggested algorithm for the management of localized prostate cancer. Current treatment options in patients with localized (non-metastatic)

Table 2. Gleason Grading System[52]

Grade	Histologic Criteria
1	Single, separate, closely packed, uniform glands with a margin delineating the edge of the tumor
2	Single, septated glands that are less uniform and more loosely arranged, with a less defined margin
3	Single, separate, but variable glands that are widely separated and have a poorly delineated margin
4	Infiltrating tumor with fused glands or large, clear cells
5	Circumscribed masses of cribiform tumor, often with central necrosis

prostate cancer include watchful waiting, radical prostatectomy, external beam radiotherapy, and brachytherapy. Cryotherapy and androgen deprivation are alternative approaches.

Table 3. Tumor-Node-Metastasis (TNM) Staging System

T Primary Tumor

- TX Primary tumor cannot be assessed
- TO No evidence of primary tumor
- TI Clinically inapparent tumor neither palpable nor visible by imaging
  - Tla Tumor incidental histologic finding in 5% or less of tissue resected (eg, transurethral resection of the prostate)
  - Tlb Tumor incidental histologic finding in more than 5% of tissue resected
  - Tlc Tumor identified by needle biopsy (eg, because of an elevated PSA)
- T2 Tumor confined within the prostate
  - T2a Tumor involves one-half of a lobe or less
  - T2b Tumor involves more than half of a lobe, but not both lobes
  - T2c Tumor involves both lobes
- T3 Tumor extends through the prostate capsule
  - T3a Unilateral extracapsular extension
  - T3b Bilateral extracapsular extension
  - T3c Tumor invades seminal vesicle(s)
- T4 Tumor is fixed or invades adjacent structures other than seminal vesicles
  - T4a Tumor invades any of the following: bladder neck, external sphincter, rectum
  - T4b Tumor invades levator muscles or is fixed to pelvic wall

N Regional Lymph Nodes

- NX Regional nodes cannot be assessed
- NO No regional node metastasis
- NI Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm, or multiple lymph nodes, none more that 5 cm in greatest dimension
- N3 Metastasis in a lymph node more than 5 cm in greatest dimension

M Metastasis

- MX Presence of metastasis cannot be assessed
- MO No distant metastasis
- MI Distant metastasis
  - MIa Nonregional lymph node(s)
  - MIb Metastasis in bone(s)
  - Mlc Metastasis in other site(s)

Prostate cancer is often a slowly progressing, indolent tumor; therefore, watchful waiting is a viable option in men with a life expectancy of less than 10 years, with localized tumor, low Gleason scores (2-6), and low PSA (less than 10 ng/mL) that does not rise substantially on serial follow-up. Reported studies suggest that watchful waiting may result in relatively low rates of death from prostate cancer (9-15%) among men with localized disease with 15-year follow-up.[54] Caution must be exercised when applying these results, as they pertain to patients who are in low-risk categories and do not apply to younger men at higher risk, who are underrepresented in the watchful waiting studies.

The ideal candidate for treatment with curative intent has clinically localized prostate cancer and a life expectancy of 10 years or more. Radical prostatectomy remains the gold standard, yet the potential side effects of impotence and incontinence deter many patients from pursuing it. Recent refinements in surgical techniques have led to decreased blood loss and improved potency (60-80%) and continence rates (> 95%), making it a more attractive treatment. The 15-year survival rates following surgery are the best of any active treatment in the published reports.[55] There are however no randomized studies sufficient to compare the potentially curative modalities.

External beam radiotherapy has been reported more often in older, less healthy patients; however, recent reports include patient groups and results more comparable to surgery. The complications of radiotherapy are related to total dosage, tumor volume treated, distribution of dosage, and fractionation schema. Treatment-related complications include impotence (~ 50%), intestinal sequelae such as tenesmus and rectal bleeding, and irritative urinary symptoms, such as frequency, dysuria, cystitis, hematuria, and urethral stricture (10-20%). At 10-year follow-up, the recurrence rates are comparable to surgery; however at 15-year follow-up, surgery offers a modest survival advantage, yet the groups are not entirely comparable.[56] Brachytherapy with palladium 103 or iodine 125 is a newer approach showing survival rates similar to radical prostatectomy at 10 years, but few patients have yet achieved adequate long-term follow-up to allow for reliable comparisons.[57] While the morbidity appears to be less than surgery, it does typically cause significant short-term urinary dysfunction, as well as some long-term erectile dysfunction (40-50%). Overall, it is a relatively new treatment, and follow-up has been limited.

An alternative approach is cryotherapy, the use of freezing to destroy prostate tissue. This is newer technology, which has recently improved through the use of ultrasound guidance, enhanced probes, and urethral warming devices.[58] Despite these improvements, complications consisting of urethral fistulas, rectal injuries, and impotence occur. The biochemical recurrence rate and persistence of cancer in follow-up biopsies appear to be higher than with radiotherapy or surgery.[59] Long-term results are needed before this technique can be advocated as an equivalent primary therapy.

Androgen deprivation, by either surgical or medical castration, is most useful as palliative therapy for extensive disease (positive lymph nodes or bone metastases) or as neoadjuvant therapy prior to radiotherapy.[60] Androgen deprivation prior to

surgery has not been shown to improve biochemical recurrence or survival and, thus, is not recommended.[61] Prostate cancer is a heterogeneous tumor composed of hormone-sensitive and hormone-insensitive cells. The degree of hormone sensitivity determines the patient's response to androgen deprivation. The Veterans Administration Cooperative studies in the 1960s and 1970s laid the groundwork for the use of palliative hormonal therapy.[62] After initiation of androgen deprivation, approximately 40% of patients will have stabilization of disease, and 20% will have continued cancer growth. Response to androgen ablation is limited. The average duration of response to orchiectomy or medical castration in patients with symptomatic metastatic prostate cancer is 36 months, and, almost invariably, these cancers ultimately become refractory to androgen deprivation.

Future Directions

The optimum management of prostate cancer remains elusive. Basic science research is currently focusing on the role of hormones, growth factors, oncogenes, tumor-suppressor genes, and apoptosis. The horizon seems bright for gene therapies aimed at treating localized prostate cancer and disseminated tumors. A variety of methods using various viruses for insertion of genes that cause tumor apoptosis either by erogenous drugs, cytotoxic T-cells, or by the tumor cells themselves are currently showing promise.[63] Clinical trials will provide important insights to help resolve current controversies concerning treatment of patients with prostate cancer and may lead to reduced morbidity among such patients.

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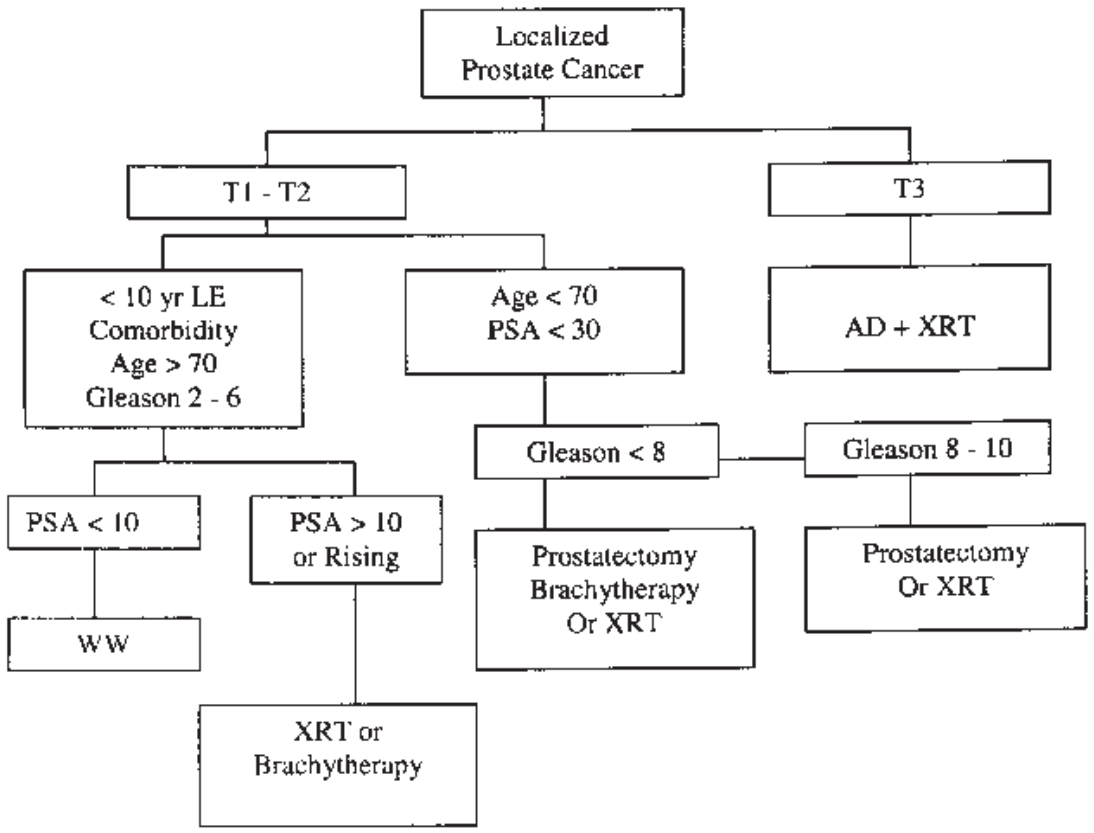
Figure 1. Prostate Cancer Management Algorithm



LE = Life expectancy
WW = Watchful waiting
AD = Androgen deprivation
XRT = External beam radiation therapy

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CME Questions

36. The most common primary visceral (nonskin) cancer in adult males in the United States is:
    a. lung.
    b. colon.
    c. prostate.
    d. lymphatic.
    e. kidney.

37. Incidence and death rates from prostate cancer are the highest for which ethnic origin of American men?
    a. Asian
    b. African
    c. Hispanic
    d. European
    e. Scandinavian

38. In men older than the age of 50 at risk for prostate cancer, the annual screening method recommended by the American Cancer Society and the American Urological Association is:
    a. PSA and DRE.
    b. TRUS and DRE.
    c. PSA and TRUS.
    d. Free PSA and DRE.
    e. Free PSA and TRUS.

39. The risk of prostate cancer metastases is increased in a patient with which one of the following?
    a. Prostate volume > 50 cc.
    b. Free PSA ratio > 25%.
    c. Total PSA > 1 0 ng/mL.
    d. PSA density < 0. 1 5 ng/mL.
    e. PSA velocity < 0.75 ng/mL/y.

40. A patient with a PSA of 6.0 ng/mL, a normal 20 g prostate on DRE, and a TRUS-guided biopsy read pathologically as Gleason 3+3/10 adenocarcinoma of the prostate has which primary clinical stage prostate cancer?
    a. Tlc
    b. T2a
    c. T2b
    d. T3a
    e. T3b

In Future Issues:

Ankle Sprains—
Robert C. Schenck, Jr., MD, and Michael J. Coughlin, MD