Prostate cancer: current concepts in diagnosis and treatment

ERIC A. KLEIN, MD

■ Improvements in early detection, staging, and treatment of prostate cancer were seen during the last decade, yet prostate cancer continues to account for significant morbidity and mortality in older men. Current diagnostic and staging techniques, surgical and nonsurgical therapy, operative complications, palliative care, and the role of screening are reviewed.

INDEX TERMS: PROSTATIC NEOPLASMS; ADENOCARCINOMA ▯ CLEVE CLIN J MED 1992; 59:383–389

ALTHOUGH PROSTATE CANCER is better understood today than it was 10 years ago, essential questions about etiology, screening, and treatment limitations remain to be addressed. This article reviews current knowledge of incidence, diagnosis, staging, and therapy, and lends perspective to the controversies surrounding prostate cancer screening and the optimal use of various screening techniques.

BACKGROUND

In 1990, adenocarcinoma of the prostate became the cancer with the highest incidence in American men, surpassing carcinoma of the lung. An estimated 100,000 new cases of prostate cancer were diagnosed, with more than 28,000 deaths.[1] Despite advances in early detection, staging, and treatment during the last decade, prostate cancer ranks third as a cause of cancer deaths in US men, behind lung and colon cancer, and still accounts for a significant level of morbidity in older men.

Little is known about the biologic origins of prostate cancer. The disparity between clinically evident cancers and the very high incidence of cancer of the prostate observed at autopsy (70% incidence in the ninth decade) remains unexplained. Also unexplained are differences in the incidence and death rates from prostate cancer across geographic and racial boundaries. The incidence of clinically detectable prostate cancer ranges from 0.8 per 100,000 in China to 100.2 per 100,000 blacks in California.[2] Mortality rates for prostate cancer also vary widely: 3 per 100,000 in Uruguay, 12 per 100,000 in Germany, 22 per 100,000 in the US, and 32 per 100,000 in Sweden.[3]

Prostate cancer has not yet been linked to potential causative factors such as diet, sexual activity, venereal disease, smoking, or environmental exposure. Because prostate cancer is usually sensitive to androgen withdrawal, one hypothesis is that high serum testosterone levels are pathogenic. One study has suggested that serum testosterone levels are higher in young blacks than in whites,[4] an intriguing observation in view of the observed higher incidence of prostate cancer in black men (lifetime risk approximately 11%) compared with white men (9%).

Recent epidemiologic studies have shown that the risk of prostate cancer is twice as high when a first-degree relative is affected, and almost nine times as high when both a first- and second-degree relative are affected.[5] Another clearly associated risk factor is age, with incidence (clinically and at autopsy) and mortality rates beginning a steep climb at age 50. The

From the Department of Urology, The Cleveland Clinic Foundation.

Address reprint requests to E.A.K., Head, Section of Urologic Oncology, Department of Urology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

occurrence of benign prostatic hyperplasia (BPH) does not increase the risk of prostate cancer.[2]

Molecular and genetic studies have yet to identify specific chromosomal abnormalities associated with prostate cancer, although data from cell lines would suggest that the short arm of chromosome 10 may be important.[6] Specific alterations in oncogene structure or function that may account for the development or progression of prostate cancer are not yet identified. One study reported that retroviral transfer of an intact retinoblastoma gene (a known "tumor suppressor" gene) into a prostate cancer cell line reversed the cell line's ability to form tumors in nude mice.[7] The prostate is rich in both growth factors and growth factor receptors, but the role of these molecules in normal prostatic growth or cancer has yet to be defined.

DIAGNOSIS

The sine qua non for the diagnosis of prostate cancer is a tissue biopsy that reveals histological evidence of cancerous prostate glands. Usually the biopsy is obtained from a nodule in the peripheral zone of the prostate detected by palpation during digital rectal exam. Occasionally an unsuspected cancer is detected in tissue removed during transurethral resection of the prostate (TURP) performed because of obstructive voiding symptoms. These cancers arise in the histologically distinct transition zone and may have a different biologic potential than cancers of the peripheral zone. Many cases of prostate cancer are suspected only when a patient is symptomatic from systemic disease; these patients typically present with back or joint pain, weight loss, fatigue, or failure to thrive without symptoms referable to the prostate and have diffuse metastatic disease apparent on bone scan. An increasing number of patients with early-stage disease are diagnosed after screening studies that demonstrate elevated serum levels of prostate-specific antigen (PSA).

Prostate biopsy

The usual method of obtaining prostatic tissue is by transrectal needle biopsy. The development of spring-loaded disposable biopsy "guns" has made this a safe and relatively painless procedure which can be performed in the office without anesthesia. Patients take a Fleet enema and an oral dose of a quinolone antibiotic at home on the morning of the procedure. Antibiotics are continued for 72 hours after biopsy. The use of fine-needle aspiration biopsy is an acceptable alternative to true needle biopsy whenever expertise in cytologic diagnosis of prostate cancer is available. However, diagnosis by needle aspiration does not permit assignment of histologic grade (see below).

Transrectal ultrasonography (TRUS) of the prostate allows precise localization of prostatic lesions and increases confidence that the observed or palpable abnormality was actually sampled. Digitally guided "blind" biopsies of palpable lesions are acceptable, provided that a repeat biopsy with ultrasonic guidance is performed if no cancer is evident on the initial tissue specimen. TRUS should always be used to identify nonpalpable lesions and to guide biopsies in men who are biopsied because of elevated PSA levels. TRUS also can be used to guide systematic random biopsies to estimate the extent and pattern of distribution of cancer within the prostate.

Histology

The diagnosis of prostatic cancer can be difficult if only a few glandular acini are present in a biopsy or if only a few glands are involved. Histologic criteria for the diagnosis of cancer include nuclear anaplasia, the presence of prostatic crystalloids, and disruption of normal acinar architecture. Invasion of perineural spaces is a common finding. Cellular and glandular atypia (prostatic dysplasia, prostatic intraepithelial neoplasia, or carcinoma in situ) are frequently associated with cancer. The isolated finding of one of these entities in a biopsy which does not contain frank cancer should lead to a more systematic examination and sampling of the prostate with repeated biopsies under ultrasonic guidance. The development of monoclonal antibodies specific for PSA and prostatic acid phosphatase (PAP) allows immunohistochemical staining of tissue samples to help confirm the prostatic origin of equivocal biopsies or metastatic lesions.

The most widely accepted grading system for prostate cancer was described by Gleason. Using this system, cancers are graded from 2 to 10 by assessing the primary and secondary architectural patterns of the malignant glandular acini. Grade 2, 3, and 4 tumors are considered well-differentiated, grades 5 to 7 moderately differentiated, and grades 8 to 10 poorly differentiated. This system is reproducible and yields some prognostic information.[8]

STAGING THE CANCER

Once the diagnosis of prostate cancer is established, a staging evaluation is indicated. Staging determines

TABLE
STAGING FOR PROSTATE CARCINOMA

Definitions:		
Primary tumor (T)		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Clinically inapparent tumor not palpable nor visible by imaging	
	T1a	Tumor incidental histologic finding in 5% or less of tissue resected
	T1b	Tumor incidental histologic finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy (eg, because of elevated prostate-specific antigen)
T2	Tumor confined within prostate	
	T2a	Tumor involves 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 prostatic 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: bladder neck, external sphincter, rectum
	T4b	Tumor invades levator muscles and/or is fixed to pelvic wall
Regional lymph nodes (N)		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	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 in greatest dimensions, or multiple lymph node metastases, none more than 5 cm in greatest dimension	
N3	Metastasis in a lymph node more than 5 cm in greatest dimension	
Distant metastasis (M)		
MX	Presence of distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Nonregional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

the extent of disease in order to define both treatment and prognosis. The American Joint Committee on Cancer Staging has recently approved an updated staging system which for the first time includes a staging classification for nonpalpable tumors suspected by elevations in serum PSA (stage T1c) (*Table*).

The distinction between stage T1a and T1b cancers is somewhat controversial. Some consider only minimal involvement (5%, or three or fewer chips) by well-differentiated tumor (Gleason score 2 to 4) as stage T1a, whereas others accept up to 10% involvement of any grade less than 8. Patients with palpably localized tumors (T2 and T3) and negative bone scans, but elevated PSA or PAP, typically prove to have extracapsular extension on pathologic analysis and illustrate the relative insensitivity of the digital rectal exam and imaging modalities in the detection of microscopic disease outside of the prostate.

Determining local extent

The local extent of prostate cancer is best determined by digital rectal examination by an experienced urologist. An assessment of the location and size of the cancer is made with particular emphasis on determining whether there are signs of local spread through the prostatic capsule into surrounding soft tissue, or invasion of the seminal vesicles or bladder neck. The use of TRUS and magnetic resonance imaging (MRI) in determining the local extent of prostatic cancer has been disappointing. A recent study from a cooperative group found that in patients with operable prostate cancer (stages T1 and T2) TRUS had only a 58% staging accuracy and MRI a 69% accuracy as measured by ability to detect cancer extending outside the prostate.[9] A new trial employing an endorectal surface coil[10] and improved imaging software which may yield superior MR images is currently underway. Computed tomography (CT) of the prostate is too insensitive to be helpful in defining the local extent of disease.[11]

Metastatic disease

A screen for metastatic cancer should include a general physical examination with special attention to the presence of lymphadenopathy, abdominal mass, and lower extremity edema. Chest roentgenography to screen for unsuspected pulmonary pathology and metastatic lesions to the lungs and ribs is also indicated. Parenchymal lung metastases from prostate cancer are typically lymphangitic in appearance and may be confused with interstitial fibrosis. An intravenous urogram will screen for hydronephrosis, invasion of the bladder base, unsuspected urologic anomalies, and metastases to the pelvic bones.

Determination of serum tumor markers is also important. An elevated PAP is highly specific for the presence of metastatic disease, but because serum levels of PAP are elevated in only two thirds of patients with metastases, the sensitivity of PAP is low. PSA is the most sensitive tumor marker for prostate cancer, although elevated levels may be detected in patients with BPH or prostatitis. When malignancy is present, serum levels of PSA are directly proportional to the volume of cancer. Currently, two commercial assays for PSA are available. The Hybritech Tandem R assay defines normal PSA levels as 0 to 4.0 ng/mL; the Yang assay defines normal between 0 to 2.5 ng/mL. A mild degree of elevation in PSA (15 to 20 ng/mL) in a patient with apparently localized prostate cancer often indicates unsuspected invasion of the prostatic capsule or seminal vesicles; higher levels almost invariably in-

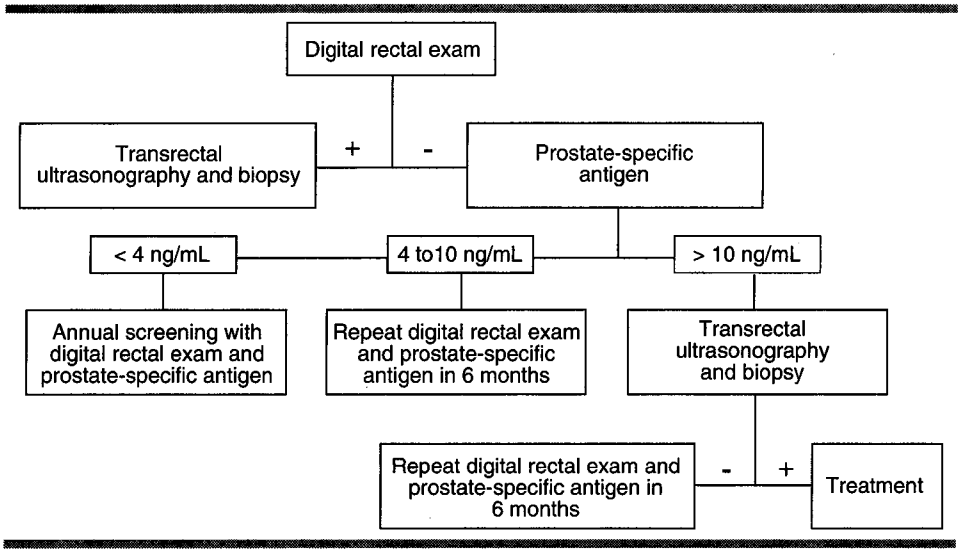

FIGURE. Practice guidelines for prostate cancer screening.

dicate periprostatic spread, nodal metastases, or occult systemic disease.

A radionuclide bone scan is performed to screen for skeletal metastases. Recent studies have suggested that the likelihood of a positive scan is low (1%) in patients with serum PSA levels by Hybritech assay below 20 ng/mL and may not be necessary in these patients.[12] CT scans are insensitive in detecting the local extent of prostatic cancer but may be useful in evaluating the pelvic lymph nodes in patients with elevated PAP or PSA. A CT scan in a patient with stage T1 or T2 cancer and normal serum markers does not usually add clinically useful information.

SCREENING FOR PROSTATE CANCER

Screening for prostate cancer has become a topic of concern both because of an increasing incidence of cancer and the availability of sensitive and noninvasive measures such as serum PSA and TRUS. Much controversy remains over how best to screen the general population, and some disagree over whether earlier detection will decrease mortality.

There are conflicting reports on whether the addition of TRUS to digital rectal examination increases the detection rate of prostate cancer. Overall the detection rate based on screening with digital exam alone is about 1.5% to 4.0%, and with TRUS 2.5% to 6.5%, although one recent study comparing digital exam and TRUS in the same population found digital exam superior by 5.4% to 4.4%.[13] Each method has limitations in detecting cancers, and each can detect cancers that the other will miss.

One problem with the digital rectal exam is the infrequency with which it is performed. In a screening program of 433 men over age 40 performed at the Cleveland Clinic in 1989 and 1990, 67% said they had not had a digital rectal exam performed in the previous year. Perhaps more alarming was that, of the 153 who reported having a general physical exam in the previous year, a digital rectal exam was included in only 56%.[14] TRUS is limited because it has a significant learning curve and because it will miss the 30% of prostate cancers that appear isoechoic rather than hypoechoic. The American Urological Association (AUA) has recognized the value of TRUS as a diagnostic procedure but has not endorsed its use for screening. I believe TRUS is most useful for evaluating patients with abnormal digital rectal exam and/or elevated PSA and for guiding biopsies, rather than as a screening tool.

Research shows that the combination of digital rectal exam and PSA assay can increase the detection rate of prostate cancer. In a study of 1,807 men with digital rectal exam, TRUS, and PSA assay (Hybritech), Cooner showed that the rate of detection of prostate cancer in men with an abnormal digital rectal exam was 12% if the PSA was under 4 ng/mL, 43% if the PSA was 4 to 10 ng/mL, and 76% if PSA was over 10 ng/mL.[15] In men with normal prostates on digital rectal exam, the corresponding detection rates were 2%, 7%, and 28%. In patients with normal digital exam and PSA under 4 ng/mL, 11 patients were biopsied for each cancer detected. The corresponding ratio for PSA between 4 to 10 ng/mL was 7:1 and for PSA above 10 ng/mL, 3:1. These data suggest that it may not be cost-effective to biopsy men with normal digital rectal exam and PSA levels under 10 ng/mL.

Based on these considerations, I use the following guidelines in my practice (*Figure*):

1. All men over age 40 undergo a screening digital rectal exam yearly. This is in accordance with AUA recommendations.

2. Serum PSA is determined in men between the ages of 50 and 70, and in younger men with symptoms suggesting bladder outlet obstruction owing to prostatic enlargement or a family history of prostate cancer.

3. Men with normal digital rectal exam and PSA levels under 4 ng/mL are followed yearly with repeat digital exam and PSA assay. Men with normal digital rectal exam and PSA levels between 4 and 10 ng/mL are reevaluated at 6 months.

4. Men with an abnormal digital rectal exam or PSA levels over 10 ng/mL undergo TRUS and biopsy. If the biopsy is positive, appropriate treatment is instituted. If the biopsy is negative, digital exam and PSA assay are repeated in 6 months; TRUS is again performed if either test has changed significantly or if the suspicion of cancer remains high.

TREATMENT

Treatment of prostate cancer is determined by clinical stage. It is axiomatic that patients with cancers confined to the prostate can be cured, while those with extraprostatic spread cannot. Practically speaking this means that stage T1 and T2 cancers are generally curable, some "small" stage T3 cancers are curable, and larger stage T3 and metastatic cancers are not curable.

Localized cancers

Older patients with stage T1a cancers are at low risk for tumor progression (12% to 15% in 8 years)[16] and may safely be followed with periodic digital rectal exam and PSA assay. Younger patients (those with at least a 15-year life expectancy) with stage T1a disease should undergo definitive therapy as described below.

Patients with stage T1b or T2 cancers are potentially curable by radical prostatectomy or external-beam radiotherapy. While recent years have witnessed a renewed interest in radical prostatectomy, its superiority over external-beam radiation in curing patients has not been established.[2] Disease-specific survival of 90% at 5 and 10 years has been reported with both surgery and radiation therapy.[2]

Radical prostatectomy

Radical prostatectomy is now commonly performed with reduced morbidity and little mortality in patients up to age 70 (and selected patients up to age 75). Modifications in the dissection of the urethra at the prostatic apex and bladder neck have resulted in the return of continence postoperatively in 50% of patients by 5 weeks and in 82% by 12 weeks.[17] Overall continence rates approach 90%, with 5% to 8% requiring one to three pads per day for stress incontinence; only 1% to 2% never achieve continence. The use of the nerve-sparing technique in selected patients can spare potency in 50% to 80% depending upon age, preoperative sexual function, and postoperative motivation.

Using the retropubic surgical approach, bilateral pelvic lymphadenectomy is performed before removal of the prostate. I proceed with prostatectomy only in those patients with negative lymph nodes as determined by frozen section examination (which has 80% accuracy). The role of radical prostatectomy with or without early androgen ablation therapy in patients with positive lymph nodes is controversial. The similar survival rates reported in patients treated with both prostatectomy and early androgen ablation therapy are mostly likely due to the endocrine therapy rather than to the prostatectomy. The added benefit of avoiding symptoms of local progression by the addition of radical prostatectomy to androgen ablation has not been proven. The use of laparoscopy to perform pelvic lymphadenectomy is currently under clinical trial, and its ultimate role in the management of patients with prostate cancer is not yet determined.

Following radical prostatectomy, patients are followed at yearly intervals. A baseline serum PSA level should be checked within several weeks of surgery. PSA should fall to an undetectable level in patients who have had complete tumor excision. Any detectable level of PSA in the early postoperative period implies the presence of residual cancer, even if the level is within the range of "normal" for the laboratory; the optimum management of these patients with observation, adjuvant radiotherapy, or androgen ablation is undefined. A rising PSA level in a patient with previously undetectable PSA usually heralds a local or distant recurrence. TRUS can be used to guide biopsies of the vesicourethral anastomosis in patients with elevated PSA levels but no palpable lesion transrectally; one study documented a 40% incidence of nonpalpable local recurrence using this approach.[2]

Radiation therapy

External-beam radiotherapy is indicated in patients who refuse surgery or have medical contraindications to surgery. Typically, patients experience some urinary urgency, rectal tenesmus, diarrhea, and fatigue during treatment; these symptoms resolve after completion of therapy. Potency can be spared in about 50% of patients treated with external-beam radiotherapy, and incontinence is rare. PSA levels which do not fall to

within the normal range within 6 months after therapy are associated with a higher incidence of local recurrence.[18] The presence of cancer on biopsy of an irradiated prostate usually heralds distant relapse. The role of salvage radical prostatectomy for radiation failures is also controversial. En bloc removal of the bladder is sometimes necessary; in instances where the prostate can be removed alone, the incontinence rate is reported as high as 50%.

Interstitial radiotherapy with ^{125}I or ^{198}Au has recently fallen out of favor because of poor long-term rates of local control. Newer isotopes implanted with the use of perineal templates are currently under investigation.

Advanced cancers

The optimum therapy for patients with stage T3 prostate cancer is not defined. The relative inability of radiation therapy to sterilize pelvic lymph node metastases coupled with a 50% incidence of nodal metastases in stage T3 lesions limits the usefulness of external-beam radiotherapy. Androgen ablation therapy is often used as an alternative. Radical prostatectomy is generally not indicated in stage T3 cancer because of a significant incidence of incomplete tumor excision. The benefits of attempting to "downstage" stage T3 cancers preoperatively with neoadjuvant antiandrogen therapy before prostatectomy remains to be proven.

At present, metastatic cancers are not curable but can be effectively palliated for relatively long periods. Surgical castration or oral estrogens have been the mainstays of treatment for metastatic cancers since the observation of Huggins and Hodges[2] that androgen deprivation has an antitumor effect. Both have documented therapeutic efficacy, and both remain reasonable treatment choices. Orchiectomy avoids problems with patient compliance and may be the least costly alternative. Diethylstilbestrol (DES) should be avoided in patients with a history of thromboembolism or cardiac disease. I begin DES therapy with 1 mg/day and titrate the dose up to 3 mg/day until serum testosterone falls to anorchic levels. Several newer agents given by injection—the luteinizing hormone-releasing hormone (LHRH) agonists leuprolide and goserelin—also suppress testicular androgen production and have clinical efficacy similar to orchiectomy. The main disadvantage of these agents is cost (approximately $4,800 per year).

The development of pure antiandrogens (cyproterone acetate, flutamide, nilutamide) has focused attention on the role of adrenal androgens in prostate cancer. Whether blockade of the 5% of circulating testosterone contributed by the adrenals is important in preventing progression of prostate cancer is uncertain. Several clinical trials that compared medical castration using an LHRH agonist vs combined "total androgen blockade" with an LHRH agonist or orchiectomy and an antiandrogen have been completed. To date the results of these trials have been mixed. The findings of the widely quoted National Cancer Institute trial[19] showing a prolonged disease-free interval and survival with combined therapy have not been corroborated by similar studies.[20] My view is that total androgen blockade is effective therapy for prostate cancer but is not proven to be clinically superior to standard therapies. In addition, while the role of total androgen blockade remains controversial, most patients with prostate cancer treated in this manner still die of their cancer. The development of effective chemotherapy or other treatment alternatives for patients who fail androgen ablation therapy of any sort still looms as an unconquered challenge.

REFERENCES

1. Silverberg E, Lubera JA. Cancer statistics, 1989. CA 1989; **39:**3.
2. Gittes RF. Carcinoma of the prostate. N Engl J Med 1991; **324:**236.
3. Catalona WJ, Scott WW. Carcinoma of the prostate. In: Walsh PC, Gittes RF, Permutter AD, Stamey TA, eds. Campbell's urology. 5th ed. Philadelphia: WB Saunders, 1986:1464.
4. Ross RK, Bernstein L, Judd H, Hanisch R, Piko M, Henderson B. Serum testosterone levels in healthy young black and white men. J Natl Cancer Inst 1986; **76:**45.
5. Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC. Family history and the risk of prostate cancer. Prostate 1990; **17:**337.
6. Klein EA. Molecular and cytogenetic events in urologic tumors. Semin Urol 1988; **6:**2.
7. Bookstein R, Shew J-Y, Chen P-L, Scully P, Lee W-H. Suppression of tumorigenicity of human prostate carcinoma cells by replacing a mutated RB gene. Science 1990; **247:**712.
8. Gleason DF. The VACURG histologic grading and clinical staging of prostatic adenocarcinoma. In: Tannenbaum M, editor. Urologic pathology: the prostate. Philadelphia: Lea & Febiger, 1977:171–198.
9. Rifkin DR, Zerhouni EA, Gatsonis CA, et al. Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi-institutional cooperative trial. N Engl J Med 1990; **323:**622.
10. Schnall MD, Lenkinski RE, Pollack HM, Imai Y, Kressel HY. Prostate: MR imaging with an endorectal surface coil. Radiology 1989; **172:**570.
11. Platt JF, Bree RL, Schwab RE. The accuracy of CT in the 19 staging of carcinoma of the prostate. Am J Roentgenol 1987; **149:**315.
12. Chybowski FM, Keller JJ, Bergstraih EJ, Oesterling JE. Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: prostate specific antigen is superior to all other clinical parameters. J Urol 1991; **145:**313.
13. Palken M, Cobb OE, Simons CE, Warren BH, Aldape HC. Prostate cancer: comparison of digital rectal examination and transrectal

ultrasound for screening. J Urol 1991; **145:**86.
14. Klein EA, Gerlach RW. Prostate examinations are overlooked. Cleve Clin J Med 1991; **58:**51.
15. Cooner WH, Mosley BR, Rutherford CL Jr., et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination, and prostate specific antigen. J Urol 1990; **143:**1146.
16. Smith JA, Cho Y-H. Management of stage A prostate cancer. Urol Clin North Am 1990; **17:**769.
17. Klein EA. Early continence after radical prostatectomy. J Urol (in press).
18. Landmann C, Hunig R. Prostatic specific antigen as an indicator of response to radiotherapy in prostate cancer. Int J Radiat Oncol Biol Phys 1989; **17:**1073.
19. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of Leuprolide with and without Flutamide in prostatic carcinoma. N Engl J Med 1989; **321:**419.
20. Klein EA. Editorial comment on: Lubric F. Medical management of prostate cancer. Drug Therapy 1989 (November).