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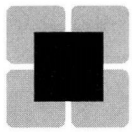

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An update on prostate cancer

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SUMMARY As screening for prostate cancer has become more common, the issues surrounding its diagnosis and treatment have grown more complex. This review surveys recent advances and controversies, including definition of risk factors, the role of screening, and current treatment strategies.

KEY POINTS African American heritage and age are risk factors for prostate cancer. There appear to be familial and hereditary forms of prostate cancer, which are separate and distinct. A link to vasectomy is speculative. Whether PSA should be used for screening remains controversial. The high incidence of occult carcinoma associated with prostate intraepithelial neoplasia dictates early re-evaluation of patients with this finding on biopsy. Observation rather than treatment may be a reasonable option for older patients or those with low-grade tumors and life expectancy of less than 10 years.

The major advantage of radiation therapy over surgery is that it is less invasive, but it is associated with a higher risk of symptomatic local recurrences. Cryotherapy should be considered an investigational technique with unknown long-term results.

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DURING THE LAST decade both the incidence and public awareness of prostate cancer have increased dramatically. With this growth have come a number of medical issues and controversies. This paper examines some of them, including: (1) the relative roles of age, race, and family history as risk factors for developing prostate cancer; (2) the proper use of serum prostate-specific antigen (PSA) assays; (3) the diagnosis of prostate cancer and the meaning of prostate intraepithelial neoplasia; (4) a new tumor staging system that has been widely adopted; (5) the debate over the treatment of localized prostate cancer, including watchful waiting, radical prostatectomy, and radiation therapy; and (6) treatment options for advanced cancers.

CURRENT TRENDS

Between 1987 and 1992, the number of radical prostatectomies performed in men over age 65 in the United States increased by 560%, from 7028 to 39 157.[1] During the same period, the number of prostate biopsies performed increased by 430%. The reasons for this expansion are many: the

development of PSA assays, transrectal ultrasonography, spring-loaded biopsy needles, widespread screening programs, increased public awareness of prostate cancer, and advances in surgical technique, which have resulted in better functional outcomes. Public awareness of prostate cancer has been particularly fueled by the deaths of several national celebrities.

An estimated 244 000 new cases of prostate cancer will be diagnosed in 1995, and 40 000 men will die of it.[2] Prostate cancer is second only to lung cancer as a fatal malignant disease in men and is likely to continue to increase in incidence as the average age of the population increases.

EPIDEMIOLOGY AND RISK FACTORS

Despite intensive efforts during the last decade to unveil the origins of prostate cancer, the molecular details of its development and progression remain poorly understood. Long-standing epidemiologic observations that age and race play an important role continue to be validated by current studies. In addition, genetic epidemiologic data have identified a cohort of families that appear to have a true hereditary form of the disease. A possible link to vasectomies remains speculative.

Age

The incidence of prostate cancer increases with age, the prevalence at autopsy being 30% in men over age 50 and 70% in men in their 80s.[3] A recent study also demonstrated that the age-adjusted incidence of invasive prostate cancer is rising dramatically—an increase of 8% in 1989, 33% in 1990, and 72% in 1991 over 1988 figures.[4] Rates of diagnosis increased for all ages beginning at age 55, with the most marked increases noted in men between the ages of 75 and 84. The increased incidence is undoubtedly due to more screening: the number of PSA tests increased fivefold to sevenfold in the five laboratories surveyed in this study. Even so, detected cases still represent only a fraction of the estimated 8 million men over age 50 who harbor cancer of the prostate. This observation highlights the continued lack of understanding of the biological characteristics of "latent" cancers and raises important issues regarding screening and treatment.

Racial differences

African Americans have a higher age-specific incidence and a higher prostate cancer death rate than Caucasians do. National data reported in 1989 suggested that the lifetime risk of developing prostate cancer is 1 in 9 in African Americans and 1 in 11 in Caucasians.[3] In one study, age-adjusted incidence rates rose by 2.7 and 3.1 per 100 000 yearly before 1989 for Caucasians and African Americans, respectively, and by 23.5 and 19.4 per 100 000, respectively, between 1989 and 1991.[4] It is unclear whether the incidence is actually increasing faster in Caucasians, or whether this group merely has better access to PSA screening and other tests.

The higher death rate in African Americans has never been adequately explained biologically. A recent autopsy study of 152 men age 50 or younger revealed premalignant lesions and incidental carcinomas of the prostate with equal frequency in both races.[5] Further, the cancerous foci were of similar size and occurred as early as the third decade in both groups. This suggests that both races are equally prone to the early development of prostate cancer but may have biologic differences in how the disease progresses.

Another interesting study compared PSA levels and pathologic stage in Caucasian and African American patients who had equal access to screening and diagnostic services within the US military system. In 264 patients who underwent radical prostatectomy, the mean preoperative serum PSA level was significantly lower in Caucasians (8.9 vs 15.2 ng/mL), and 50% of Caucasians had organ-confined disease compared with only 39% of African Americans.[6] In another study, in men with localized prostate cancer, there were no differences in mean age or preoperative PSA levels between the races. However, more African Americans than Caucasians had locally advanced disease (68% vs 57%) and positive margins (55% vs 35%), both of which impart a worse prognosis.[7]

Family history

Family history is another well-known risk factor for prostate cancer. However evidence indicates that the risk may take two forms, a familial cancer and a less common hereditary prostate cancer. In 1990, a large epidemiologic study demonstrated that a man's risk of developing prostate cancer is approximately twice that of the general population if he has a first-degree relative with the disease, and is almost nine times as high when both a first and

second degree relative are affected (*Table 1*).[8] More extensive epidemiologic data have now identified a cohort of families with a hereditary form characterized by early age at onset and autosomal dominant inheritance. Hereditary prostate cancer should be suspected if prostate cancer occurs in multiple generations or in multiple family members, especially if the age of onset is less than 55. Men in these families have an approximately 50% risk of cancer, compared with a 13% risk in the general population.[9] Molecular genetic studies have suggested that the gene responsible for hereditary prostate cancer is highly penetrant and that 88% of gene carriers develop prostate cancer by the age of 85. Hereditary prostate cancer is distinguished from the familial form, which occurs in patients with a positive family history but who do not exhibit early onset. However, pathologic analysis has failed to demonstrate substantial differences among the hereditary, familial, and sporadic forms.[10] Further, hereditary prostate cancer does not appear to be associated with other cancers.[11]

Vasectomy

Several epidemiologic studies have demonstrated a higher risk of prostate cancer in men who have had a vasectomy, with a relative risk of approximately 1.5, rising to approximately 1.8 by 20 years after vasectomy.[12–14] No currently accepted biological hypothesis can explain this, and the link remains speculative. The American Urological Association suggests discussing the risk with men considering vasectomy and that vasectomy be considered a risk factor for the purposes of screening.

SCREENING

Screening for prostate cancer remains controversial because no studies have documented a decrease in the mortality rate in screened populations. However, PSA testing began to be used in screening programs only approximately 5 years ago. In contrast, prostate cancer is relatively indolent; survival rates must be measured in 10- and 15-year intervals. Therefore, at least another 5 to 10 years of clinical experience and completion of ongoing randomized trials such as the National Cancer Institute-sponsored screening trial for cancers of the prostate, lung, colon, and ovary (the PLCO trial) will likely be necessary to answer this question.

TABLE 1
RELATIVE RISK OF DEVELOPING PROSTATE CANCER ACCORDING TO FAMILY HISTORY*

Relatives affected	Relative risk
One second-degree	1.7
One first-degree	2.0
Two first-degree	4.9
One first and one second-degree	8.8
Three or more first-degree	10.9

*Adapted from Steinberg et al, reference 8

Role of digital rectal examination, PSA, and ultrasonography

Those who advocate screening generally agree on which tools to use. In a recent multicenter study, more than 6000 men underwent digital rectal examination, PSA testing, and transrectal ultrasonography. The overall detection rate was highest for PSA testing (4.6%), followed by digital rectal examination (approximately 3.2%).[15] The positive predictive value of PSA testing was superior to that of digital rectal examination (31.5% vs 21%), and the combination of an elevated PSA level and abnormal findings on rectal examination had a positive predictive value of 48.5%. A combination of abnormal ultrasonographic findings, an elevated PSA value, and abnormal findings on rectal examination carried a positive predictive value of 55%. However, if patient comfort and convenience and the variability in interpretation of ultrasonographic studies are considered, these data suggest that a combination of rectal examination and serum PSA testing may be most cost-effective.

What is a normal PSA?

Some controversy has arisen over whether 4 ng/mL (by Hybritech assay) is the appropriate upper limit of normal for serum PSA. Oesterling[16] has suggested using age-specific PSA cutoff levels to increase the test's sensitivity in younger patients and its specificity in older patients (*Table 2*). This would decrease the number of biopsies performed in older men, who are more likely to have benign prostatic hypertrophy and who may be more appropriate candidates for observation alone. The overall number of biopsies would be approximately the same, but there would be fewer biopsies in men in their 60s who have PSA values between 4.0 and 4.5 ng/mL. Several analyses have suggested that approximately 5%

TABLE 2
AGE-SPECIFIC PROSTATE-SPECIFIC ANTIGEN (PSA) RANGES*

Age	Normal PSA range, ng/mL
40–49	0–2.5
50–59	0–3.5
60–69	0–4.5
70–79	0–6.5

*Adapted from Oesterling et al, reference 16

to 15% of cancers in this age group would be missed if the higher age-specific PSA cutoff were used.[17,18] However, whether waiting until the PSA level reaches 4.5 ng/mL in these patients would result in more-advanced cancer (which might not be curable) is not clear. Several ongoing prospective trials are evaluating this issue.

When should screening begin?

The American Urological Association, the American College of Surgeons, and the American Cancer Society suggest that men with no risk factors undergo yearly digital rectal examination and PSA testing beginning at age 50. Men with risk factors such as a family history of prostate cancer or African ancestry are advised to begin screening at age 40. No data are available regarding the age at which screening should stop, and none of these organizations have specifically commented on this issue. Current clinical practice would dictate, however, that patients who have less than a 10-year life expectancy or who are unlikely to be candidates for definitive therapy if they do have prostate cancer should not be screened, regardless of age.

Screening, mortality, and clinically significant tumors

Although no studies have demonstrated that screening leads to a decrease in the mortality rate, several studies with surrogate endpoints suggest that screening detects clinically important cancers that are organ-confined in a higher proportion of patients than in nonscreened populations. In contemporary series of radical prostatectomies, long-term disease-free survival rates with persistently undetectable PSA levels are obtained more frequently in cancers that are organ-confined.[19] Catalona[20] reported on a series of 2000 men with newly diagnosed prostate cancer detected by digital rectal examination alone, a single PSA determination, or serial PSA determinations. The incidence of locally advanced or metastatic cancer was highest in cancers detected by rectal examination alone, followed by those detected with a single PSA determination. Use of serial PSA measurements as a trigger for biopsy significantly increased the detection rate of organ-confined (and therefore potentially curable) cancers. On the other hand, the incidence of latent cancers (which may not require treatment) was highest in the serially screened population, but these still accounted for fewer than 10% of the detectable cancers. Another study, in patients with prostate cancer detected solely on the basis of an elevated PSA value (stage T1c), also suggested a higher incidence of organ-confined cancers in this population.[21]

The National Prostate Cancer Detection Project recently reported on 2999 men who underwent serial screening for 5 years with digital rectal examination, PSA testing, and transrectal ultrasonography. Of the cancers detected, approximately 5% were clinical stage C or D, leaving approximately 95% in the curable category.[22] This stands in stark contrast to the 1982 American College of Surgeons' patterns-of-care study, in which approximately 50% of patients with newly diagnosed prostate cancer had incurable disease at the time of presentation.[23] Further, a recent computer-based decision-analysis model concluded that PSA screening actually resulted in a net harm as assessed by predicted quality-adjusted survival.[24] However, this study was based on only a single screening event (rather than serial events), did not consider actual patient evaluations of quality of life, and underestimated the rate of metastasis in the untreated population.

Screening: recommendations

Should men be screened for prostate cancer? This question is not likely to be settled until there are clear data suggesting a reduction in mortality in screened populations. However, evidence continues to mount that serum PSA has impressive value in predicting clinically significant tumors. In a prospective evaluation of stored plasma samples from the Physicians' Health Study, Gann and colleagues[25] demonstrated that single abnormal PSA determinations detected nearly 80% of all aggressive cancers diagnosed within 5 years in 366 men. Further, only 96 (8.7%) of 1098 men who remained free of prostate cancer during the 10-year follow-up had false-positive PSA elevations, for a specificity of greater than 90%. In addition, the risk of prostate cancer

increased with PSA concentration, even in the normal range (< 4.0 ng/mL). Compared with PSA values less than 1.0 ng/mL, PSA values of 1.01 to 1.5 ng/mL carried a relative risk of 2.2, increasing to a relative risk of 8.6 with PSA values of 3.01 to 4.00 ng/mL.

Although these findings are impressive, efforts are underway to further improve the specificity of PSA testing and reduce the number of unnecessary biopsies performed. One area of investigation is to define the expected rate of increase ("PSA velocity") for men with age-related increases in prostatic size or benign prostatic hypertrophy. Several studies have suggested that any increase in PSA of more than 0.75 ng/mL per year increases specificity to greater than 90% and should trigger a biopsy; lesser increases are more likely due to benign prostatic hypertrophy and can be followed.[26] Other studies have suggested using a cutoff of a 20% increase in PSA per year, so that for an initial PSA of 1.4 ng/mL, an increase of even 0.3 ng/mL in a year should trigger biopsy.[27] Both of these approaches are constrained by the need for repeated PSA determinations at 1.5- to 2-year intervals and will therefore be most useful for serially screened men who have initial PSA levels in the normal range.

Another promising approach to eliminating unnecessary biopsies is the determination of bound vs unbound ("free") PSA levels in serum. Men with benign prostatic hypertrophy have higher levels of free PSA, while men with cancer have more PSA bound to alpha-1 antichymotrypsin. Although further study is necessary to define the optimal cutoffs based on prostatic size, initial data suggests that a free/total PSA ratio of < 0.15 is more likely associated with cancer and warrants biopsy.[28,29]

These studies suggest that PSA screening has a high level of sensitivity for identifying clinically significant cancers. Refinements in PSA assays and interpretation of PSA changes over time are likely to further increase this test's specificity and reduce the rate of false-positive results and unnecessary biopsies. In my view, these advances should lead to greater acceptance of routine screening of asymptomatic men, even while we await long-term studies on the effect of screening on mortality.

DIAGNOSING PROSTATE CANCER

Biopsy and histology

The sine qua non for the diagnosis of prostate cancer remains an aspiration cytologic study or tissue biopsy that reveals histological evidence of cancerous acini. In years past, the most common indication for prostate biopsy was a palpable induration or nodule on rectal examination; now, the most common reason is an elevated serum PSA value.

Transrectal ultrasonography is useful in guiding a biopsy needle to a precise location within the prostate. In the presence of a palpable nodule or induration, ultrasonography may be unnecessary. However, it is extremely useful in random but directed sextant biopsies in patients with elevated PSA levels and no palpable abnormalities and in obtaining specimens from the anterior transition zone, which harbors approximately 10% to 20% of tumors. In experienced hands, transrectal ultrasonography may be used to guide biopsies without the need for anesthesia.

Histologic criteria for the diagnosis of prostate cancer have not changed during the last several years. These include nuclear anaplasia, prostatic crystalloids, and disruption of the normal acinar architecture. Invasion of perineural spaces is common. The most widely accepted grading system is that of Gleason, which assigns a summed grade of 2 to 10 according to the primary and secondary architectural patterns of the malignant glandular acini. Tumors of grade 2 to 4 are considered well differentiated; 5 to 7, moderately differentiated; and 8 to 10, poorly differentiated.

Prostate intraepithelial neoplasia (PIN)

Much attention has been focused in the recent urologic and pathologic literature on PIN. Histologic evidence strongly suggests that high-grade PIN is a premalignant form of prostate cancer that corresponds to carcinoma in situ.[30] PIN consists of dysplasia and proliferation of the normal lumenal cell layer lining prostatic ducts and acini. Histologic features include cellular crowding, variability in nuclear size, hyperchromatism, and enlarged nuclei.[30–33] These features are indistinguishable from invasive adenocarcinoma, and PIN is distinguished from cancer only by a preserved basal cell layer, which is lost in cancer. A three-tiered grading system for PIN has been described,[33] but clinical experience has shown it difficult to distinguish between medium- and high-grade PIN. Most pathologists report only the presence of PIN in low or high grade.[33,34]

PIN is observed in 30% to 70% of prostates that contain cancer.[33,35] The histologic evidence to suggest that PIN is a precursor to invasive adenocarcinoma is, in brief: (1) Low-grade PIN occurs as early

TABLE 3
AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR PROSTATE CANCER

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 or vesicles
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 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 or nodes
	M1b	Bone or bones
	M1c	Other site or sites

TABLE 4
POSITIVE PREDICTIVE VALUES OF VARIOUS STAGING TOOLS FOR PROSTATE CANCER BASED ON REPORTED VALUES

Stage	Positive predictive value, %			
	Digital rectal examination	Transrectal ultrasonography	Computed tomography	Magnetic resonance imaging
Capsular confined	42	46	41	50
Capsular extension	80	76	75	86

as the third decade of life and increases in incidence with age in autopsy series of men who died of other causes. PIN precedes histologic evidence of cancer by 10 to 20 years.[31,33] (2) PIN occurs significantly more frequently in glands that contain adenocarcinoma than in those that do not, and multifocal cancers are typically associated with multifocal PIN.[33–39] (3) High-grade PIN is closely associated with adenocarcinoma, as demonstrated by a low incidence in noncancerous glands, a high incidence in cancerous glands, predominant occurrence in the peripheral zone where most cancers arise, and microscopic proximity to established cancers. Immunohistochemical studies have demonstrated several cases of high-grade PIN harboring microinvasive cancers.[33–39] (4) Finally, PIN exhibits molecular phenotypic characteristics intermediate between those of normal epithelium and adenocarcinoma, including a higher incidence of aneuploidy, increased expression of cytokeratins, decreased expression of lectins and vimentins, and mutant expression of P53 and EGFR compared with normal glandular epithelium.[36–42]

PIN: recommendations

The appropriate clinical management of high-grade PIN found on needle biopsy in the absence of invasive adenocarcinoma is undefined. However, the high incidence of occult carcinoma associated with PIN as well as the histologic proximity of PIN to invasive cancer should dictate an early re-evaluation of such a patient. This should include needle biopsies in the area of the gland from which the PIN was found as well as multiple biopsies from other portions of the gland. Because the rate of progression of PIN to

invasive cancer is unknown, patients with PIN should undergo rectal examination, PSA testing, and repeat biopsies at 3-to-6-month intervals. Definitive therapy (radiation therapy or radical prostatectomy) should be withheld until a definite histologic diagnosis of cancer has been established.

STAGING

New system

A new staging system (*Table 3*), proposed in 1991, has been widely adopted. This system integrates the older ABCD and TNM staging systems and creates a new clinical stage (T1c), which represents cancer diagnosed by needle biopsy performed because of an elevated serum PSA level in the absence of a palpable nodule. A recent analysis of 157 men with clinical stage T1c disease who underwent radical prostatectomy demonstrated that they had a pathologic extent of disease intermediate between clinical stages T1a and T2.[21] Eighty-four percent had biologically significant tumors for which treatment with curative intent could be justified.

Staging problems

Discrepancies between the clinical and pathologic stages (as determined by step-section analysis after radical prostatectomy) remain a significant problem. Clinical understaging is the more common problem and occurs in approximately 30% to 40% of patients. However, clinical overstaging also occasionally occurs, further contributing to difficulties in deciding who are candidates for definitive therapy. Recent studies have shown that men with well- or moderately differentiated cancers confined to the capsule or specimen have extended long-term disease-free survival rates after surgery.[19] The clinical challenge, therefore, is to identify these patients who would benefit from surgery (and patients with more extensive disease, who would not).

All currently available tests have relatively high false-negative rates and therefore low positive predictive values (*Table 4*). A recent study evaluating an endorectal surface coil for high-resolution magnetic resonance images of the prostate and surrounding structures recorded a staging accuracy of 74% in advanced disease, 91% in depicting involvement of the seminal vesicle, and 68% overall.[43] Failure to recognize microscopic extracapsular disease accounts for most staging inaccuracies with all of the available tests.

TABLE 5
RISK OF BONE METASTASES ACCORDING TO SERUM PROSTATE-SPECIFIC ANTIGEN LEVEL*

Prostate-specific antigen level, ng/mL	No.	Positive scan	
		No.	(%)
≤ 10	218	0	(0)
10.1–20	99	1	(1)
20.1–50	99	7	(7)
50.1–100	60	23	(38)
> 100	56	40	(71)

*Adapted from Chybowski et al, reference 44

Staging advanced cancers

Two controversies currently concern the staging of more-advanced disease. In 1992, Chybowski et al[44] reported that the likelihood of bone metastases in patients with PSA values of less than 20 ng/mL was extremely small (*Table 5*). This has led some urologists to suggest omitting bone scans from the metastatic evaluation in patients with PSA values less than 10 or 20 ng/mL, which would significantly reduce the cost of staging. However, occasional patients with bone metastases despite low serum PSA levels would needlessly be subjected to surgery or radiation therapy. Such patients are rare, and in my experience, usually have poorly differentiated tumors. Therefore, in my practice, I usually omit bone scans for men with PSA values less than 20 ng/mL, unless the cancer is of high grade.

The second controversy relates to the need for pelvic lymphadenectomy. Screening programs, by detecting patients with earlier-stage disease, are contributing to a "stage-migration effect." Several investigators have noted a reduced prevalence of positive nodes at the time of radical prostatectomy (approximately 5%, compared with up to 30% in stage B disease in the era before PSA testing).[45] Several published nomograms purport to predict the likelihood of node-positive disease on the basis of palpable extent, tumor grade, and serum PSA level, and some experts have suggested omitting pelvic lymphadenectomy in patients with a low likelihood of nodal metastases according to these nomograms, even in patients undergoing a retropubic approach.[46] In our experience, in the most recent 245 patients who underwent pelvic lymphadenectomy before radical prostatectomy, the overall node-positivity rate was 6.5%.[47] Factors predictive of lymph node metastases included advanced clinical stage (ie, grade T2b or T2c), serum PSA levels above 10

ng/mL, and a Gleason grade of 6 or greater. Of patients who had none of these factors, 2.2% had nodal metastases. Further, frozen section examination failed to detect cancer in the lymph nodes in 45% of cases. These findings suggest that routine pelvic lymphadenectomy before definitive therapy for presumed localized disease is optional in patients at low risk.

These observations have also lent support to a resurgence in the perineal approach to radical prostatectomy, which had fallen out of favor because it necessitates a separate abdominal incision to sample the lymph nodes. Extended experience with laparoscopic pelvic lymph node dissection has added to the growing popularity of perineal prostatectomy. However, even in the most carefully selected series of laparoscopic lymphadenectomies, the node-positive rate was only approximately 25% to 30%, and one could argue that 70% to 75% of patients have been subjected to an unnecessary procedure.[48] Furthermore, in at least one recent series, the complication rate during laparoscopic pelvic lymphadenectomy exceeded the node-positive rate.[49]

The obvious advantage of omitting a pelvic lymph node dissection, regardless of surgical approach, is reduced cost and morbidity. Whether these advantages outweigh the prognostic information that accrues from knowing whether the patient has nodal metastatic disease (which could affect the decision to perform prostatectomy) is a philosophic judgment that, in an era of cost containment, may be deemed unessential.

The future of staging

Efforts are underway in a number of other areas to define better the pathologic extent of prostate cancer before definitive therapy, on the basis of the histologic grade, the number of cores containing cancer on multiple prostate biopsies, and the amount of cancer present in each core.[50] Computer-based decision-analysis models with a neural network design are also under investigation. Several investigators have used the polymerase chain reaction technology to detect PSA-producing cells in the systemic circulation or bone marrow of patients undergoing radical prostatectomy, and a whole-body monoclonal antibody scan for staging is also under investigation. Further experience will be necessary to validate these tools and determine their clinical utility.

TREATING LOCALIZED PROSTATE CANCER

Few issues in urology have generated as much debate as the treatment of patients with clinically localized cancer. This debate is fueled by reports that observation alone, radical prostatectomy, and radiation therapy all result in overall survival rates comparable to that in the general population. This attests to the slow progression of some prostate cancers, effective treatment of at least some of the more aggressive cancers, and the high rate of mortality due to competing causes of death in the over-60 population, in which most cancers are diagnosed. This controversy is unlikely to be settled any time soon, given the difficulty of performing head-to-head randomized trials of different treatments. For example, a Southwest Oncology Group study comparing definitive external-beam radiation therapy vs radical prostatectomy was closed early because of an inability to recruit a sufficient number of patients. Hope springs eternal, however, and several randomized trials are underway comparing observation vs radiation therapy, hormonal therapy vs radiation therapy, and radical prostatectomy vs observation (the PIVOT Trial). Whether these trials can be successfully completed and generate meaningful results remains to be seen.

Observation (watchful waiting)

In men with localized prostate cancer, several nonrandomized series indicate that, without therapy, the long-term cancer-specific death rate ranges from 10% to 15%.[51–53] However, these series represent highly selected patients who are not representative of the population generally chosen to undergo radical prostatectomy, and they ignore the morbidity associated with metastatic disease. For example, in the series reported by Johansson,[52] 48% of the patients had stage A tumors at presentation, and 66% had low-grade tumors. Sixty-two percent of the patients were older than age 70 and 17% were over 75; the mean age was 72. This contrasts markedly with patients currently undergoing radical prostatectomy in the United States, where only approximately 20% have stage A tumors, approximately 25% have low-grade cancers, the mean age is in the low 60s, and only 10% to 25% are over age 70. In Scandinavia, approximately two thirds of all patients with prostate cancer present with locally advanced or metastatic disease and are excluded from observational studies by immediate hormonal

therapy.[51,52] In a study from Memorial Sloan-Kettering Cancer Center, the disease-specific mortality rate was approximately 15% at 10 years,[53] but this study included only 75 of 4000 patients with prostate cancer seen during a 30-year period, who were chosen because they had stable disease by rectal examination for 1 year prior to study entry.

TABLE 6
META-ANALYSIS OF OUTCOMES WITH VARIOUS FORMS OF TREATMENT FOR LOCALIZED PROSTATE CANCER*

Therapy	Metastases	Prostate cancer deaths	Other deaths
Deferred	25.1†	16.8	49.9
Radical prostatectomy	12.6	7.0	9.9
X-ray therapy	29.0	38.2	36.3

*Adapted from Adolfsson et al, reference 55
†Weighted number per 1000 patient-years

Two meta-analyses regarding observation have also been published. Chodak et al[54] found an 80% 15-year survival rate in patients with grade 1 or 2 disease, contrasting with a 25% 15-year survival rate for those with high-grade disease. However, the progression rate was as high as 25% in the low-grade tumors at 15 years, and none of the observational studies to date have taken into account the morbidity or cost of treating the patients with advanced disease. In another meta-analysis, Adolfsson et al[55] compared the likelihood of metastatic disease and deaths due to prostate cancer in reported series of observation, radical prostatectomy, and radiation therapy. They concluded that radical prostatectomy was associated with the lowest incidence of metastases and the fewest deaths due to prostate cancer (*Table* 6), even though the percentage of patients with high-grade cancers was twice as high in the radical prostatectomy and radiation therapy groups as in the observation group.

Observation: recommendations

Together, these data suggest that observation is a reasonable treatment option for older men or those with low-grade tumors and life expectancy of less than 10 years. Younger men with early stage tumors or high-grade tumors with a longer projected period of risk should be candidates for curative therapy.

Radical prostatectomy

Surgeons have now gained extensive experience with the technique of radical prostatectomy popularized by Walsh in the early 1980s, which, in selected patients, allows better control of the dorsal venous complex, a more careful apical dissection, and preservation of the penile nerves subserving erections. Excellent long-term disease-free survival rates in large numbers of patients treated with this technique have now been reported, and further modifications in the apical dissection may result in earlier return of urinary control and shorter hospital stay.[19,55,56]

Survival. Walsh and Partin[19] have recently reported an 8-year follow-up of 955 patients who underwent radical prostatectomy for clinical stage T1 or T2 disease. Of patients who presented with organ-confined disease or capsular penetration but negative surgical margins and a Gleason grade of 6 or less, more than 90% had undetectable PSA levels 8 years later. The survival rates were much lower for patients with higher-grade tumors (Gleason grade 7 or greater) or low-grade tumors with positive surgical margins. Both seminal vesical invasion and node-positive disease impart limited long-term disease-free survival. Overall, at 10 years, 70% of patients had undetectable PSA levels, 23% had isolated PSA elevations, 4% had clinical local recurrence, and 7% had metastases.

Incontinence and sexual function. Several centers report that urinary continence returns completely in more than 90% of patients, the rest having mild degrees of stress incontinence.[19,55,56] The overall surgical mortality rate is approximately 0.5% or less.[19,57,58] Overall potency rates vary from 30% to 70% depending upon patient selection, the experience of the surgeon, and whether potency is judged by the physician or by the patient.[19,59] The rate of return of urinary control and the overall continence rate also seem to be related to age.[19,55,56] Screening programs that incorporate age-specific PSA limits will likely result in radical prostatectomy being increasingly performed in younger patients with organ-confined disease, which should further minimize complications from this procedure.

Cost. More recent efforts have focused on decreasing the cost of performing radical prostatec-

tomy. In one recent study, overall cost was reduced by 41% and mean length of stay from 5.7 to 3.6 days.[57] At the Cleveland Clinic, a decrease in the median length of stay from 8 to 5 days resulted in a cost reduction of 36%.[58] This was achieved by more aggressive perioperative management (outpatient bowel preparation, admission directly to the operating room, rapid postoperative ambulation, and reinstitution of oral intake and oral analgesics on the day after surgery) and routine removal of surgical drains at 72 to 96 hours. The current length of stay has been further reduced to a median of 2 or 3 nights with no increase in the overall complication rate.[60]

Laparoscopic procedures. The development of laparoscopic lymphadenectomy has rekindled interest in the perineal approach to radical prostatectomy. Several series have attested to the efficacy of this approach. The reported advantages include less blood loss, a shorter length of stay, and a shorter operative time. However, the perineal approach entails a longer operative time when laparoscopic lymphadenectomy is performed, and current hospital lengths of stay are similar for both the retropubic and perineal approach.[57,58,61] Further, some investigators have questioned whether a true nerve-sparing procedure can be performed via the perineal approach, and the reported potency rates after perineal prostatectomy bear out this concern.[61]

This approach remains a reasonable option for experienced surgeons in patients in whom postoperative potency is not a concern. Nomograms that predict the likelihood of positive lymph nodes will obviate laparoscopic lymphadenectomy in selected patients, further lessening the morbidity and time associated with the perineal approach.

Radiation therapy

Radiation therapy became popular during the 1960s as an alternative to surgery for the treatment of localized prostate cancer, owing to the morbidity associated with older techniques of radical prostatectomy and technical improvements in the delivery of radiation therapy. In several series, the 10- and 15-year survival rates of treated patients were similar to those for age-matched controls. A recent National Institutes of Health consensus conference concluded that, before screening became widely used, 10-year survival rates were similar after radical prostatectomy or external-beam radiation therapy.[62]

The only prospective, randomized trial to compare the two treatments demonstrated a higher progression-free survival rate with radical prostatectomy.[63] This trial has been criticized on several fronts, however: only about 50 patients were included in each arm, and many were not treated according to randomization. Further, the results of radiation therapy in this trial were not as good as those reported at other centers contemporaneously. Some series that reported worse results for radiation therapy than for radical prostatectomy included older patients with worse performance status and patients with higher-grade, more locally advanced tumors who were not deemed good candidates for surgery.[62] These factors illustrate the importance of comparing the results of these two treatments on a stage-for-stage basis and incorporating modern staging criteria, including preoperative PSA levels.

Several recent studies have examined the likelihood of achieving a normal PSA level after radiation therapy according to pretreatment serum PSA levels. Zagars[64] reported that all patients with normal pretreatment PSA levels (< 4 ng/mL) were free of disease at a median follow-up of 17 months. In contrast, pretreatment PSA levels of greater than 40 ng/mL were associated with a 50% rate of clinical failure. Patients with PSA levels between 4 and 40 ng/mL had intermediate results. Schellhammer[65] has reported similar results.

New approaches. Recent efforts have focused on decreasing the toxicity of radiation therapy. One promising approach is conformal or three-dimensional radiotherapy, which employs rigid patient immobilization and three-dimensional CT-guided target planning via a box technique with four or more fields.[66] Using this technique, the margin of treatment may be reduced to as little as 1.5 cm in all fields, which permits delivery of higher doses to the target volume while limiting toxicity to adjacent normal organs. Preliminary reports note less acute toxicity and better disease-free survival (based on PSA levels) using this approach.[62,66]

Another new approach involves the implantation of palladium or iridium interstitial seeds via the perineum.[67] Advances in transrectal ultrasonography and the development of perineal templates permit more uniform seed distribution and dose than was possible by the retropubic approach and contribute to this technique's popularity. One small, early study demonstrated a 5-year, disease-free survival rate similar to that after radical prostatectomy.[67] Further, perineal brachytherapy may be asso-

ciated with less acute toxicity than standard external-beam radiotherapy.[67]

Radiation therapy vs surgery. From a clinical perspective, the major advantage of radiation therapy is that it does not cause urinary incontinence or entail surgery. However, radiation therapy is associated with a 40% to 60% incidence of impotence.[62] The major clinical disadvantage of radiation therapy is difficulty in treating local recurrences. Salvage radical prostatectomy is associated with a 10-fold higher complication rate than standard radical prostatectomy, a 30% to 50% risk of incontinence, and a long-term disease-free survival rate of approximately 25%.[68] It remains to be seen whether survival rates can be improved by performing salvage radical prostatectomy earlier, using PSA testing to detect recurrence after radiation therapy.[69]

Cryosurgery

Cryosurgery is the in situ destruction of tumors through freezing. Cryogenics dates to 1877, when Gillet and Pictet described the liquefaction of oxygen; the liquefaction of nitrogen followed in 1895. The modern age of cryosurgery began in 1961, when Cooper developed the first closed cryoprobe, which circulated cold nitrogen gas.[70] Cryosurgical ablation of prostate cancer, first described in the 1970s, offered the potential advantages of rapidity, bloodlessness, and a lower risk of incontinence than the prostatectomies performed in that era.

Addonizio[71] reported that 229 high-risk patients with prostate cancer who underwent open perineal cryotherapy with visual and tactile monitoring had documented stage-for-stage survival rates comparable to those for patients who underwent radical prostatectomy or radiation therapy; other reports concurred. Nevertheless, this technique was abandoned because of unacceptably high morbidity rates (including a 25% incidence of urethrocutaneous or urethrorectal fistulas), the need for prolonged bladder drainage of necrotic prostatic tissue, and the lack of an accurate internal monitoring technique to assure that all areas of tumor were destroyed while surrounding normal tissue was spared.[71,72] In 1982, Ando[73] reported using transabdominal ultrasonography to monitor cryoprostatectomy. Further technical advances have rekindled interest in prostatic cryoablation: high-frequency transrectal linear-array ultrasonographic probes that permit real-time two-dimensional imaging of the prostate, improved systems for delivery of freezing temperatures to the tumor, the simultaneous use of multiple probes, and urethral warming devices that minimize urethral injury and tissue sloughing. Several pilot studies in animals have examined the feasibility of percutaneous prostate ablation. One study, in five dogs, demonstrated that transrectal ultrasonography can accurately depict the extent of single cryolesions. Pathologic examination showed that the prostate appeared markedly sensitive to freezing, and all tissues exposed to freezing underwent coagulative necrosis.[74]

To date, more than 1000 cryosurgical procedures have been performed in humans with prostate cancer, although only a single study evaluating this technique has been published.[75] In this study, 55 patients underwent 68 treatments with simultaneous transrectal ultrasonographic monitoring.[76] The overall rate of acute major complications was 10%; two patients developed urethrorectal fistulas and three experienced urethral sloughing. Minor and spontaneously resolving complications included perineal ecchymosis, penile edema, and ileus. Thirty-five percent of patients retained potency after treatment. At 3 months, 83% of patients had negative biopsies, and the mean serum PSA value was 1.5 ng/mL. A recent update of this series reported a positive biopsy rate at 1 year of 33% in 39 patients with clinical stage T1 or T2 tumors.[77] Other trials of cryotherapy in locally advanced tumors or radiation failures are also underway.

Recommendations. At present, cryotherapy should be considered an investigational technique with unknown long-term results and complication rates. I believe cryotherapy should be restricted to patients who are not good candidates for cure by standard techniques, such as those with clinical stage T3 (locally advanced) tumors or those for whom radiation therapy has failed. We are currently treating such patients in experimental protocols. More extensive experience and longer follow-up will be necessary to determine what role cryotherapy will have in treating localized disease.

TREATMENT OF ADVANCED CANCERS

Clinical stage T3

The optimum therapy for stage T3 prostate cancer has not yet been 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.[3,62] Androgen ablation therapy is often used as an alternative. Radical prostatectomy is generally not indicated in stage T3 cancer because of the frequent impossibility of completely excising the tumor.[19] Preoperative (neoadjuvant) antiandrogen therapy to "downstage" stage T3 cancers has received much recent interest. The results of several randomized trials evaluating this approach will be reported shortly. At present, this approach remains investigational.

Management of metastatic cancers

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 cancer since the observation of Huggins and Hodges that androgen deprivation has an antitumor effect. Both treatments have documented therapeutic efficacy and both remain reasonable choices. Orchiectomy avoids problems with patient compliance and may be less costly. Diethylstilbestrol (DES) should be avoided in patients with a history of thromboembolic or cardiac disease. In usual clinical practice, luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide and goserelin have replaced DES because of their lack of life-threatening toxicity. These agents also effectively suppress testicular androgen production and have clinical efficacy similar to orchiectomy. Their main disadvantage is cost.

The role of androgen ablation (incorporating medical or surgical orchiectomy) combined with oral antiandrogens such as flutamide remains controversial. In 1989, a National Cancer Institute cooperative group study demonstrated a survival advantage with combined therapy compared with leuprolide alone of 7 months for all patients and 20 months in patients with minimal metastatic disease confined to the axial skeletal and ribs.[78] This trial has been criticized because of the small number of patients in each of the minimal-metastatic-disease arms (41 patients each) and because of questions about whether the observed survival advantage was simply due to blockade of the early surge of testosterone secretion due to LHRH agonists in the combined arm. This issue remains controversial and is unlikely to be settled until the results of a large randomized Southwest Oncology Group trial comparing orchiectomy with or without flutamide are reported. In view of the previously reported stage migration associated with screening for prostate cancer, this trial may be the last opportunity to answer this question as the incidence of newly diagnosed stage D cancer is markedly reduced in serially screened populations. At present, maximal androgen ablation remains a reasonable option for patients with minimal metastatic disease, but the issues of cost, toxicity, and quality of life need to be addressed further before it can be universally recommended.

Management of hormone-refractory disease

Treatment of patients who have progressive disease after hormonal therapy remains problematic. Approximately 50% of patients treated with combined androgen ablation therapy for a minimum of 18 to 24 months demonstrate a withdrawal syndrome upon cessation of flutamide.[79] This withdrawal phenomenon is currently unexplained but appears to be associated with a survival advantage. Therefore, the first step in managing patients with hormone-refractory disease who have been receiving combined androgen therapy is to discontinue the oral antiandrogen. Palliative radiation therapy, including the systemic use of strontium 89 in patients with diffuse bone metastases not amenable to localized radiation therapy, is of benefit in some patients.

Cytotoxic chemotherapy, long used in hormone-refractory disease, has been generally ineffective. Recent work has demonstrated some hope for combinations of microtubular inhibitors that have synergistic effects. The combination of etoposide or vinblastine and estramustine has been associated with a response rate of approximately 40% to 50% as defined by a reduction in PSA or in bidimensionally measurable disease.[80] The toxicity of these combinations is acceptable, and these agents may be given on an outpatient basis. Furthermore, the antigrowth factor suramin has also been recently reported to show significant activity against prostate cancer: survival increased in patients whose serum PSA values decreased by more than 75% during treatment, and responses in soft tissue disease have been remarkable.[81] Although neither suramin nor combinations of microtubular inhibitors are curing large numbers of patients at present, these responses are encouraging and warrant further study.

SUMMARY

A definitive answer to whether screening for prostate cancer is worthwhile will have to wait

several more years. In the meantime, the widespread efforts of clinicians have already changed the profile of patients undergoing biopsies and prostatectomies. Earlier detection, better preoperative staging, and improved surgical and radiotherapy techniques are making a difference, which I believe will be reflected in better functional outcomes and decreased mortality.

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