PROSTATE CANCER SCREENING ARGUMENT

DOES IT REALLY ENHANCE OUTCOME?

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"Illusions of knowledge are the obstacles to discovery." -Daniel J. Boorstin

"... nothing improves the performance of an innovation as much as lack of controls." - Meunch

"Prostate cancer is a disease that many die with, not of." - Anon

"Is cure possible for whom it is necessary, and is cure necessary for whom it is possible?" -Willet Whitmore

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During the past decade, an increasing number of men, without symptoms referable to the prostate gland, have been subjected to various procedures to detect prostate cancer. These include blood tests for prostate specific antigen (**PSA**) levels, digital rectal examination (**DRE**) and even transrectal ultrasound (**TRUS**). In the majority, the first two are performed or ordered by internists and other primary care physicians. Although patients with abnormal findings are usually referred to a urologist, it is incumbent upon the primary physicians to understand the implications of such testing (screening) and further evaluation (specific diagnostic procedures and potential therapeutic intervention). Various cancer control organizations differ on their recommendations for PSA based prostate cancer screening (1-3). The American Cancer Society recommends annual DRE beginning at age 40, annual PSA and DRE screening for men over age 50 and beginning PSA screening in high risk groups (African-Americans and strong family history) at age 40. The recommendations are endorsed by the American College of Radiology and the American Urologic Association. The US Preventive Services Task Force recommends against routine screening and feels this should be tailored to the individual. The Canadian Task Force on the Periodic Health Examination does not recommend routine screening. A widely quoted decision analysis concluded that screening of asymptomatic men for this disease is not supported by existing data (4). Questions have been raised as to whether health insurance should pay for PSA analysis for this purpose (5).

Screening is defined as a means of detecting disease early in asymptomatic individuals with the goal of decreasing morbidity and mortality.

It is generally agreed that certain conditions should be met before mass population screening can be justified (6-8).

1. The disease should represent a significant public health problem.
2. A screening approach must exist that has adequate sensitivity, specificity and predictive value.
3. A preclinical, asymptomatic or non-metastatic phase should be detectable. The diagnostic procedure(s) should be safe, reliable and acceptable to the patient.
4. Curative potential should be significantly greater in early compared to later stages of the disease.
5. Interventional treatment of screened cases should decrease *cause specific mortality* rates.

Opponents of prostate cancer screening argue several points: that conditions 4 and 5 , and possibly 2, have not been proven; that 1/2 to 2/3 of men with abnormal screening tests will be subjected to an unnecessary biopsy, perhaps on multiple occasions; that cost will be excessive and resources could be used for other purposes; that legal issues could arise. Supporters believe that the above conditions have been sufficiently demonstrated to warrant the process; that 90% of men with an elevated PSA will develop clinical prostate cancer in 10 years (9); that early intervention can cure the disease (10).

The purpose of this discussion is to evaluate the above 5 conditions from the perspective of an internist to determine what we know and do not know about mass screening for prostate cancer in men.

THE DISEASE SHOULD REPRESENT A SIGNIFICANT PUBLIC HEALTH PROBLEM.

It has been estimated that over 41,000 men will die of prostate cancer in this country in 1996. Estimates also indicate that over 317,000 men will be diagnosed with prostate cancer in 1996 (11-16) (Fig 1). It is the tenth leading overall cause of death. The disease represents the fourth most common cause of cancer deaths and is the second leading cause in men and is approaching the death rate from breast cancer in women (Fig 2). In addition, the rate of increase in prostate cancer deaths is second only to lung cancer in women (Fig 3).

As is true of many malignancies, the incidence increases with age. As the US life expectancy has increased, so have deaths from prostate cancer. The increase in deaths due to prostate cancer is partly due to the expanding population of males over age 50. However, there has also been an absolute increase in the annual death rate from prostate cancer, rising from .09% of males over 50 in 1985 to a projected 0.13% in 1996 (Tbl 1).

ANNUAL DEATHS AND DIAGNOSES FOR PROSTATE CANCER

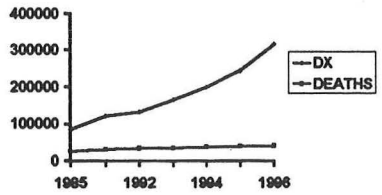


Figure 1

CANCER DEATHS BY SITE AND SEX

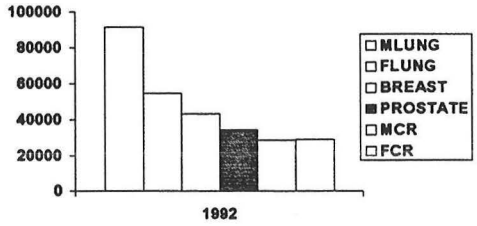


Figure 2

Another important observation is that the rate of increase of diagnoses of prostate cancer is progressively rising faster than the death rate. The ratio of diagnoses to deaths in 1985 was slightly over 3 to 1 and this will rise to nearly 8 to 1 in 1996 (Tbl 1).

ANNUAL RATES OF DIAGNOSIS AND DEATH FOR PROSTATE CANCER IN MEN OVER 50 YEARS OF AGE

	1985	1996	% Increase
% Diagnosed	0.31	1.02	229
% Deaths	0.09	0.13	44

Table 1

This is almost certainly due, in part, to a greater number of men being given screening studies as a part of their routine health maintenance. This is supported by the observations at one university medical center where there has been a total reversal of the proportion of men found to have prostate cancer who were referred to the Urology Department because of an abnormal DRE versus an elevated PSA (17) (Fig 4). One caveat however: other than non-melanoma skin cancers, prostate cancer has less effect on average years of life lost per individual dying from the disease than any other cancer (18).

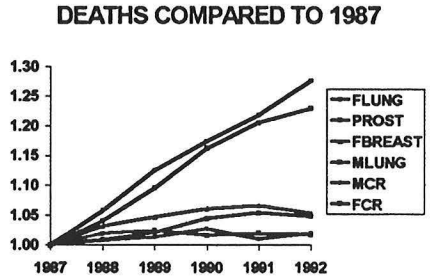


Figure 3

Conclusion: The disease represents a significant cause of morbidity and mortality in males over age 50. The mortality rate is rising as the average life expectancy increases. It is justified to explore screening approaches that could reduce the impact of prostate cancer as a public health problem.

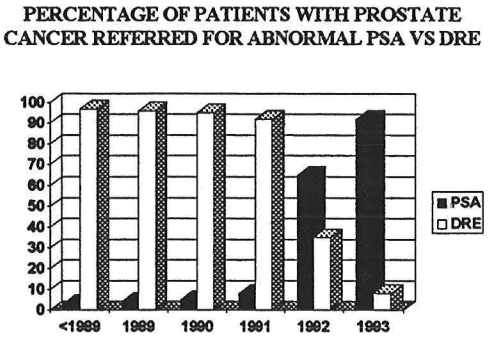


Figure 4 Ref 17

A SCREENING APPROACH MUST EXIST THAT HAS ADEQUATE SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUE.

The development of a blood test for **PSA** accelerated the enthusiasm for screening for prostate cancer. PSA is a serine protease formed almost solely by prostatic epithelial cells. It is secreted into the seminal fluid. Its physiologic role appears to be liquefaction of the seminal coagulum (19). It is a member of a family of glandular or tissue kallikreins. It has 82% sequence homology with one of these, human glandular kallikrein 1 (H-GK1) and their respective genes are closely linked on the long arm of chromosome 9 (20,21). It circulates in blood in at least three molecular forms; free, complexed with α_2-macroglobulin and bound to α_1-antichymotrypsin. The latter is the predominant form and is enzymatically inactive (22). The level in the seminal plasma is approximately 10^6 higher than the blood. This suggests a

significant barrier to access (23). Serum elevations are found in most men with clinically diagnosed prostate cancer. It may also be elevated in benign prostatic hypertrophy, acute prostatitis and prostatic trauma. It has been suggested that elevation of serum levels in BPH may be in part, a function of coexistent prostatitis or prostatic intra-epithelial neoplasia (PIN) (24). PSA is also expressed to a lesser extent in poorly differentiated carcinomas than well differentiated tumors (25). The blood level is also a function of the volume of prostatic epithelium (26,27). With more recent assay techniques, approximately 20-25% of patients with BPH will have an elevation.

The serum PSA, DRE and TRUS are the candidate screening tools of importance. Numerous studies have been published evaluating these parameters alone and in combination for the detection of prostate cancer (28-31). The sensitivity and specificity of these individual examinations are the least helpful in determining screening approaches, since calculations of the values requires the knowledge of the prevalence of prostate cancer in the population being tested. In most studies, the number of cancers detected were considered to be the true prevalence. Since the strategies utilized to detect cancer were varied, so were the presumed proportions of patients with cancer. Table 2 gives approximate values for the sensitivity and specificity of these tests. Obviously the ranges are wide due to the variable prevalence of prostate cancer that was assumed.

SENSITIVITY AND SPECIFICITY OF INDIVIDUAL SCREENING EXAMINATIONS

Procedure	Sensitivity (%)	Specificity (%)
DRE	55-70	89-97
TRUS	71-92	41-80
PSA	60-70	50-90

Table 2

Of greater importance is the positive predictive value (**PPV**) of a screening test or combination of tests, ie the proportion of patients with a positive test(s) who are found to have the disease. In addition, the cancer detection rate (**CDR**) is of interest. This value is the percentage of subjects in a screened population who are found to have cancer. If one increases the detection rate the screening strategy may be more valid.

For purposes of illustrating and comparing results of screening for prostate cancer, I have chosen three large prospective trials. They were selected because they were large in number of subjects, represented a generally healthy population of men, and employed significantly different strategies for recommending prostate biopsies (30,32-38). The studies are summarized below and are referred to by the highlighted words under investigators.

Investigators: Washington University School of Medicine, **St. Louis** (37)
Eligibility: Ambulatory, 50 years or older
Exclusions: History of prostate cancer or prostatitis

Recruitment: Lay press release requesting participation
Number entered: 10,251 over 3 years
Study Design: Serum PSA. If elevated (>4.0 ug/L), performed DRE and TRUS. If either were abnormal or suspicious, recommended TRUS guided needle biopsies. If PSA normal or TRUS and DRE were normal, repeat PSA at 6 month intervals. Repeat same procedures.
Treatment: Determined individually by urologist and patient.

Investigators: American Cancer Society National Prostate Cancer Detection Project (**ACS-NPCDP**). 10 institutions including hospitals, cancer centers and private clinical practices. (30,32-36)
Eligibility: Healthy, age 55 to 70 years
Exclusions: Previous suspicion of prostate cancer, previous prostate cancer, previous prostate surgery.
Recruitment: Public service announcements and promotions.
Number entered: 2999 over 5 years.
Study Design: PSA, DRE and TRUS performed. If DRE or TRUS abnormal or suspicious, DRE-TRUS guided biopsies recommended. PSA not used to determine biopsy recommendation (although a few patients underwent biopsy for rising or very high PSA). If DRE and TRUS normal, annual re-evaluation using same studies and recommendations.
Treatment: Determined individually by urologist and patient.

Investigators: 6 University medical centers sponsored by **Hybritech and NCI.** (38)
Eligibility: 50 years or older.
Exclusions: History of prostate cancer, acute prostatitis or UTI.
Recruitment: Advertisements in lay media.
Number entered: 6630 over 17 months.
Study Design: PSA and DRE. If PSA elevated (>4.0 ug/L) or DRE suspicious, DRE-TRUS guided needle biopsies recommended. If PSA and DRE normal, no further evaluation.
Treatment: Determined individually by urologist and patient.

If one examines the PPV of each of the three screening tests *when the other two are normal,* it is clear that the PSA has the most reliability: 21% versus 7% for DRE and 8% for TRUS (fig 5). This finding can be attributed to the fact that the TRUS is not specific enough and the DRE tends to be operator dependent.The overall positive predictive value of an elevated PSA for prostate cancer is in the range of 30-40% (39). In the largest screening study, employing a strategy of biopsy for any PSA >4.0 ug/L, the PPV was 31.5% (38). Table 3 demonstrates the

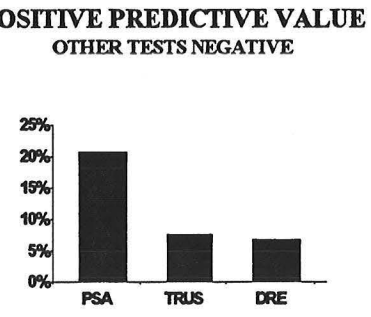


Figure 5

positive predictive value and the estimated cancer detection rate for individual tests and various combinations of tests in the three example studies. The estimated cancer detection rate is derived from the true detection rate in those subjects agreeing to be biopsied and the assumption that the detection rate in those refusing biopsy, with the same findings, would be comparable. This value indicates the largest number of cancers that would have been detected, by the given strategy, if there had been complete compliance with the study protocol.

RESULTS OF POTENTIAL STRATEGIES FOR PROSTATE CANCER SCREENING

Strategy	% Abnormal	PPV (%)	CDR (%)
DRE +	7.0	32.4	2.3
	14.8	21.4	3.2
DRE + &/or TRUS +	19.8	21.7	3.5
PSA + and	8.9	34.4	3.1
DRE + &/or TRUS+	8.5	39.6	3.4
PSA +	14.8	31.5	4.7
PSA + or DRE +	25.8	22.6	5.6

Table 3

These data would suggest that a PSA based screening strategy gives a higher cancer detection rate. However, 20-30 % of the cancers detected in the Hybritech/NCI and ACS-NPCDP had PSA levels of 4.0 ug/L or less and, therefore, using the PSA alone misses a significant number of tumors.

On the other hand, problems arise with the "false positive" PSA if a strategy of screening subjects annually with the test, and performing biopsies on those with an elevated value, is employed, as recommended by the American Cancer Society. Numerous negative biopsies will be performed and increased anxiety may occur in subjects without identifiable cancer. Therefore, several approaches are being evaluated in an attempt to increase the specificity of the PSA measurement.

PSA Velocity. This method measures the rate of change in the PSA over time, either as an absolute value or percentage increment. Published studies demonstrate significant discrepancies (37,40-44). At this time, PSA velocity has not been convincingly shown to be useful.

PSA Density. This method (also called PSA index) divides the PSA level by the volume of the gland determined by imaging techniques. Again, disagreement exists over the value of this approach (45-49). The potential problems with this measurement has been reviewed (39). Presently, there is no consensus for its use in screening for prostate cancer.

Age-Specific Cutoff Values. The widely used cutoff level of 4.0 ug/L is based on the 95% confidence interval in men without evidence of prostatic disease (50). Because the serum PSA increases with age, this method uses different cutoff values for the PSA, based on age, as an

indication for biopsy. The studies demonstrate that this approach does increase the PPV but at the expense of lowering the cancer detection rate, missing what appear to be clinically important tumors (49,51-53). It has been suggested that rather than using such a procedure, the decision to screen be based on the potential life expectancy of the patient, and if detection is warranted, then use the same cutoff level of 4.0.

PSA Forms: As noted above, PSA circulates in several forms. It has been noted that the free form makes up a greater proportion of the total in men without prostate cancer. This has led to looking at techniques to compare the PSA form distribution. It is too early to determine the potential for this method (39). (See p. 22).

Requiring a Second Test Abnormality: This modification is the strategy used in the St. Louis screening trial.

Table 4 demonstrates the impact of using different PSA levels or requiring other tests to be abnormal on the PPV, CDR and the percentage of detected tumors which are stages A-B (organ confined). The importance of stage of cancers detected by screening will addressed in the next section.

RESULTS OF RESTRICTIONS TO AN ELEVATED PSA AS AN INDICATION FOR BIOPSY

Restriction	PPV (%)	CDR (%)	% Organ Confined
PSA > 4.0	31.5	4.7	66.9
PSA + and DRE +	48.5	1.9	59.3
PSA => 10	52.9	1.4	45.2
PSA DRE TRUS all +	54.7	1.0	55.8

Table 4

It is apparent that such limitations increase the positive predictive value, but at the expense of detecting fewer malignancies and finding more that are stage C or D.

Conclusions: PSA based screening produces the highest cancer detection rates. When the DRE is also used as a detection test in conjunction with the PSA, the detection rate is maximal. However, 50-75% of biopsies performed will not detect a tumor. Attempts to improve the specificity of the PSA result in improved PPV but at the expense of lower detection rates and a tendency to a higher proportion of advanced disease. At present, the sensitivity, specificity, and PPV are not optimal, but adequate, for testing the role of PSA based prostate cancer screening.

A PRECLINICAL, ASYMPTOMATIC OR NON-METASTATIC PHASE SHOULD BE DETECTABLE. THE DIAGNOSTIC PROCEDURE(S) SHOULD BE SAFE, RELIABLE AND ACCEPTABLE TO THE PHYSICIAN AND PATIENT.

As demonstrated above, several studies exploring the question of screening for prostate cancer have demonstrated the ability to detect the disease in men who have no symptoms referable to their prostate gland. In fact, Catalona et al. found that the positive biopsy rate was equivalent in symptomatic and asymptomatic subjects (38). A confounding problem exists, essentially peculiar to prostate cancer, when looking at these results, however. The question is whether the cancers detected in asymptomatic subjects (or symptomatic persons under screening conditions) are clinically relevant. This question arises from the observation that the prevalence of prostate cancer at autopsy is much greater than the number of patients who were diagnosed with prostate cancer prior to the introduction of screening tests. Early studies demonstrated that approximately 30% of males over age 50 had prostate cancer detectable at autopsy that was not clinically recognized. The frequency increased with age (54) (Tbl 5).

FREQUENCY OF PROSTATE CANCER AT AUTOPSY

Age	% with Cancer
40-49	<5
50-59	29
60-69	30
70-79	40
80-89	67

Table 5 **Ref 54**

In the pre-screening era, this projected to a lifetime risk of developing autopsy cancer that was over 4 times the risk of developing clinical cancer and 14.5 times the risk of dying from the disease (Tbl 6)(55). Attempts have been made to determine what features of prostate cancer imply that the tumor has potential clinical importance. There are features which clearly characterize symptomatic and progressive disease and serve to differentiate it from clinically irrelevant "autopsy cancer" (Tbl 7). However, these properties actually represent extremes. The majority of cancers fall between these limits and present a spectrum of abnormalities. Based on these observations, it has been estimated that approximately 20% of cancers detected at autopsy possess features that

LIFETIME RISKS FOR PROSTATE CANCER IN A MAN AGE 50 IN 1985

	Lifetime Risk (%)	Ratio
Autopsy Cancer	42	14.5
Clinical Prostate Cancer	9.51	3.3
Death from Prostate Cancer	2.89	1

Table 6 **Ref 55**

FEATURES THAT CHARACTERIZE TYPICAL CLINICAL CANCER AND AUTOPSY CANCER

	CLINICAL	AUTOPSY
Volume	Large	Small
Grade (Dominant)	Moderate/Poor (Gleason 3-5)	Low (Gleason 1-2)
Pattern	Invasive, proliferative	Noninvasive
Flow Cytometry	Aneuploid	Diploid
Serum PSA	Elevated	Normal
Zone of Prostate	Peripheral	Transition

Table 7 **Ref 55**

would have eventually resulted in clinically symptomatic and potentially fatal disease (55). These calculations predict that about 6% of men over age 50 **may** harbor clinically unrecognized "important" malignancy (Fig 6).

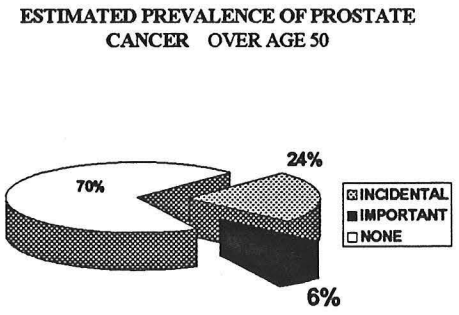


Figure 6 **Ref 55**

Tumor Grade: Of the features listed in table 7, one of the most important is the tumor grade. It is generally accepted that the Gleason system is most applicable to clinical outcomes. The system is based upon the glandular pattern of the tumor at low power. There are 5 glandular patterns of differentiation (1-5, 1 being most differentiated). A prostate cancer tends to be heterogeneous in pattern. Therefore, a Gleason score can be given which is the sum of the dominant and second most prevalent patterns (eg. 2+5=7). Prognosis tends to be dependent on the combination of patterns existing. In the literature, Gleason grading may be expressed just as the dominant pattern (possibilities 1-5) or the Gleason score (possibilities 2-10). Tables 8 and 9 list some examples of the impact of glandular grade on tumor behavior and clinical outcome (56-59). Another point from these tables is that long followup is necessary to judge the natural history of lower stage prostate cancer. Figure 7 demonstrates the Gleason score distribution of a large series of patients undergoing radical prostatectomy for clinically diagnosed prostate cancer (56-59) and compares it to the grades found in

PROSTATECTOMY SPECIMENS AND GLEASON SCORE

Pathology	Gleason Sum			
	5	6	7	8-10
Capsule Penetration (%)	16	24	62	85
Positive Margins (%)	20	29	48	59
Mean Tumor Volume (cc)	2.2	2.7	5.1	4.0
Seminal Vesicle + (%)	1	4	17	48
Node Metastases (%)	1	2	12	24

Table 8 **Ref 56-59**

RISK OF PROGRESSION AFTER PROSTATECTOMY (Seminal Vesicles and LN Negative)

Prostatectomy Specimen		Risk of Progression (%)	
		5 Years	10 Years
Gleason Sum	2-4	0	4
	5-6	3	19
	7	25	50
	8-10	43	66
Organ Confined-neg Margins	5-6*	1	8
Organ Confined-neg Margins	7	3	32
Capsular Penetration neg Margins	5-6*	2	23
Capsular Penetration neg Margins	7	17	52

* No pattern 4

Table 9 **Ref 56-59**

patients whose cancer was diagnosed in the three screening study examples. There is a reasonably similar grade grouping between the clinically diagnosed and screening diagnosed tumors. As will be seen for stage distribution, when TRUS is utilized as a primary indicator for recommending biopsy, the proportion of low grade tumors is greatest. When PSA is utilized as a screening parameter, the grade distribution most approaches that of clinically diagnosed malignancies. It is also of interest that when only T1c tumors (non-palpable lesions usually detected by PSA testing) are evaluated after prostatectomy, nearly 90% are moderately differentiated (Gleason scores 5-7). This study employed PSA as the primary screening modality to detect T1c cancers (58).

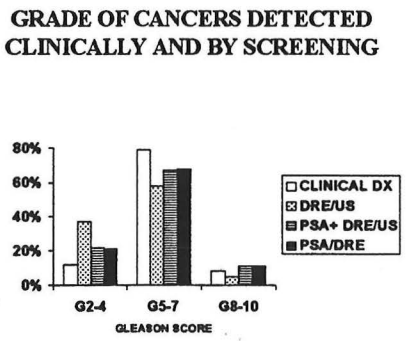


Figure 7

Tumor Stage: If, as proponents of screening for prostate cancer believe, treatment of earlier stage disease is more effective, then screening strategies must detect a greater proportion of tumors at lower stage than the standard approach of diagnosis when symptoms dictate evaluation. Several staging systems have been employed over time for prostate cancer. The system used will differ among publications. The appendix lists the standard. The primary focus when dealing with the screening premise is whether a tumor is **organ confined**. These are T1-T2 tumors without nodal (N0) or distant (M0) metastases.

ESTIMATED PATHOLOGIC STAGE DISTRIBUTION FOR CLINICALLY DIAGNOSED PROSTATE CANCER

	PATHOLOGIC STAGE		
% of Patients	TNM	AUA	AJCC
30	TXNXM1	D2	IV
20	TXN1-3M0	D1	IV
10	T3-4N0M0	C1,2	III-IV
30	T1b-	A2,B1-2	I-II
10	T1aN0M0	A1	0

Table 10 Ref 55

They are stage A-B or I-II lesions. Additionally, the stage is defined as *clinical* (stage prior to surgery) or *pathologic* (stage following prostatectomy). Utilizing published data of clinical presentation and clinical/pathologic staging (60-68), Scardino has estimated the stage distribution of prostate cancer detected on clinical grounds and treated by standard modalities. (55) (tbl 10). These data suggest that only about 30% of prostate cancer detected on clinical grounds will be stage A2-B when pathologically examined. These are the stages (organ confined potentially fatal

tumors) for which prostatectomy is deemed to have its greatest utility. In comparison, the approximate pathologic stage distribution of cancers detected with the first screen (prevalence cancers), in the three illustrative screening studies, is shown in fig 8. Of note, well over 90% of the screening detected tumors were clinically organ confined. There is clearly a stage shift in the screened populations. The number of organ confined cancers (A1-B) appears to be a function of the strategy utilized to recommend biopsy. Where both PSA and DRE are done, and biopsy is performed if either is abnormal, the number of possibly ""incidental" (A1) cancers is minimized and the proportion of A2 and B tumors is greatest. Where an abnormal TRUS is sufficient to perform a biopsy, the proportion of incidental tumors is large. Employing the PSA as a first screen and then using DRE + TRUS to indicate a biopsy results in a stage distribution intermediate to the other two. As noted in the discussion of PPV and CDR, 20-30% of cancers detected in the Hybritech/NCI and ACS-NPCDP had normal PSA values. Nevertheless, based on pathologic stage and/or Gleason grade, 70-80% of those cancers were considered to be clinically "important" cancers. Therefore, a strategy which requires that the PSA be elevated may miss 10-20% of tumors that should be detected in a screening program.

STAGE OF CANCERS DETECTED CLINICALLY AND BY SCREENING

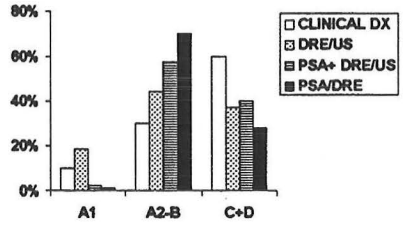


Figure 8

Data on serial screening is less reliable. In the ACS-NPCDP study there was a trend for the pathologic stage of cancers treated by prostatectomy to shift further towards organ confined stages, however the data is based on a total of 103 prostatectomies in 5 years (47 performed in the initial screening year). There was poor compliance to serial screening by the subjects over the ensuing 5 years. In the St. Louis study, based on a larger number of prostatectomies, there was no significant change in pathologic stage over the three year period of observations.

The primary screening tests (PSA and DRE) are certainly acceptable and low cost. TRUS and DRE directed needle biopsy utilizing a spring loaded device is the procedure that has been utilized in most recent studies to make the diagnosis of prostate cancer (69,70). Careful documentation of potential adverse effects of the procedure is infrequent. In one study, utilizing a prospective assessment protocol, the technique was found to have only minimal morbidity and no mortality in nearly 400 patients (71). The side effects

COMPLICATIONS OF TRUS GUIDED PROSTATE BIOPSY

Complication	% of Patients
Hematuria >2 Days	13
Hematospermia >2 days	9
Hematochezia >2 days	3
Pain	7
UTI	1-4

Table 11 Ref 71

are listed in table 11. None required hospitalization. Nevertheless, patient acceptance, based on perception, has been a problem in published screening studies. Non-compliance with the protocol due to refusal of recommended biopsy has ranged from 13-32% (32,37,38). One technical limitation of this technique is that the Gleason grade of tumors, examined after prostatectomy, may be underestimated on the biopsy specimen up to 20% of the time (72). This must be kept in mind when making management decisions based on this biopsy parameter.

Conclusions: Prostate cancers detected by PSA based screening appear to have a stage distribution that has a greater proportion of earlier stage tumors than detected clinically in symptomatic men. Gleason grades appear similar in both settings. The proportion of "incidental" or autopsy-type cancers is not certain but probably low if TRUS is not used as a screening modality. The initial screening tests are acceptable. The diagnostic test is generally safe, but has proven to be moderately problematic from the patients perspective.

CURATIVE POTENTIAL SHOULD BE SIGNIFICANTLY GREATER IN EARLY COMPARED TO LATER STAGES OF THE DISEASE.

To address this issue, it is necessary to define the term "cure" as it applies to malignant disease. The most definitive interpretation is to permanently eradicate the disease. In assessing this outcome, the evaluation of time to recurrence is utilized. If at some time point, no further patients demonstrate tumor recurrence, ie. the freedom from relapse curve becomes flat, then a curative outcome for the remaining patients is accepted. Classical examples of this result are seen with surgically treated tumors such as colo-rectal cancer and non-small cell lung cancer, as well as chemotherapy and/or radiation treated tumors such as Hodgkin's disease, large cell lymphoma, testicular germ cell tumors and childhood acute lymphoblastic leukemia. In these situations, there appears to be a finite time beyond which no further relapses are seen. Such a conclusion requires a large number of cases and adequate long-term followup of the majority. In terms of prostate cancer, it is generally accepted that patients presenting with clinical stage D disease cannot be cured. It is estimated that approximately 60% of pathologic stage C patients (mostly T3 without seminal vesicle invasion) will have a 10 year cancer specific survival and a 25% chance of no recurrence during their lifetime. However, the term cure is frequently applied, by some investigators, to the outcome of radical prostatectomy for a proportion of patients presenting with clinically organ confined prostate cancer (10). Table 12 and fig 9 demonstrate the freedom from relapse in one series, with the longest published follow-up, after radical prostatectomy, in men with clinically organ confined disease (stages T1-2N0M0). This series from Mayo clinic consisted of 3170 patients with a mean follow-up of over 5 years and observation of 12% at least 15 years (73). It is apparent that there is a continuous relapse pattern for all 3 "T" stages through at least 15 years. Figure 10 compares this group, with all T stages combined (#2), to another series purporting to show a curative out come for nearly 80% of patients with clinically organ confined cancer undergoing prostatectomy (#1) (10). In this series there were 546 patients and the mean follow-up was 2 1/2 years with a median of 20 months. Similar patterns of recurrence are seen for the first 2-3 years. The flattening of the curve could definitely be a

OUTCOMES FOLLOWING RADICAL PROSTATECTOMY FOR CLINICALLY ORGAN CONFINED PROSTATE CANCER

Clinical Stage	#	10 Year (%)			15 Year (%)		
		NED	Cause Specific Survival	Overall Survival	NED	Cause Specific Survival	Overall Survival
T1	226	70	95	75	62	85	65
T2a	897	56	90	74	43	84	59
T2b,c	2047	47	88	76	37	79	59

Table 12 Ref 73

function of only a small number of patients being actually observed in the 5-10 year period which is interpreted as continuous freedom from relapse. Examination of other published series illustrates the same phenomenon. Continued relapses are seen during those periods in which a majority of the patients were at risk for the event, including time periods of 5-10 years (74-76).

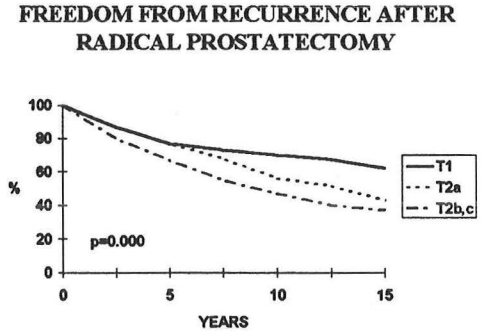


Figure 9 Ref 73

An alternate practical definition of "cure" is that the disease does not recur during the patient's lifetime and he/she dies of co-morbid conditions in complete remission. A classical example of this phenomenon is female breast cancer, especially stage I. To conclusively demonstrate this phenomenon, at some time point, the overall survival curve should fall below the relapse curve. It is difficult to ascertain from published data what proportion of patients undergoing prostatectomy expired from co-morbid conditions without evidence of recurrence of cancer. Figures 11-13 and table 12 illustrate data from the Mayo clinic series for three "T" stage groups. At no time is this criterion satisfied, although it is approaching that situation for clinical T1 lesions.

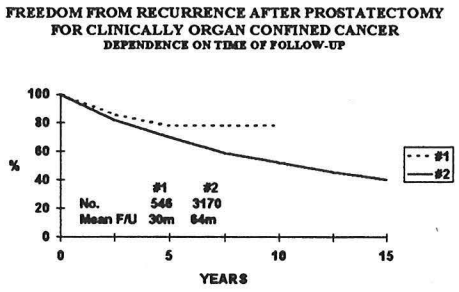
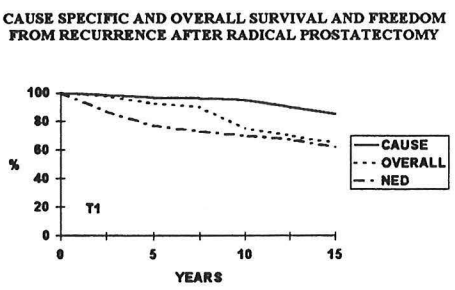


Figure 10 Ref 10,73



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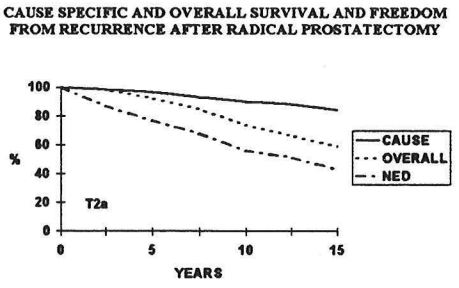

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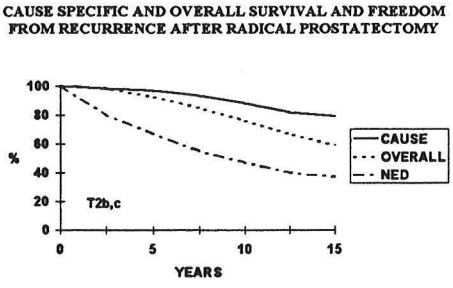

Figure 13 Ref 73

Two other considerations should be emphasized from these studies, however. First, the present measure utilized for relapse includes clinical evidence of distant metastases or local-regional recurrence *as well as* a rising PSA value (which typically falls to nearly 0 if the prostate and all macroscopic cancer is resected). Certainly, distant metastases or measurable local-regional recurrence may produce morbidity requiring palliative measures. However, just an increased PSA would be asymptomatic. Figure 14 displays the overall survival and freedom from detectable relapse (excluding solitary rises in PSA) for patients with clinical T1 tumors undergoing radical prostatectomy in the Mayo Clinic series. Beyond 10 years, the overall mortality does exceed the recurrence rate. Proponents of prostate cancer screening invoke this in support of the process. The proportion of T1 tumors detected in PSA based screening is higher than in the clinically

diagnosed setting since non-palpable tumors diagnosed by needle biopsy (T1c) are frequently detected.

As noted previously and in a recent report, approximately 90% of T1c tumors are felt to be clinically important based on grade, size, pathologic stage and flow cytometry (58,97). In patients with T2a and T2b,c disease, the overall survival and clinically detectable recurrence rates become essentially equal at 15 years (not shown). It is not the intent of this review to discuss the relative roles of surgery versus radiation therapy for early stage prostate cancer. It is worth pointing out that radiation therapy results demonstrate the same pattern of continued progression but

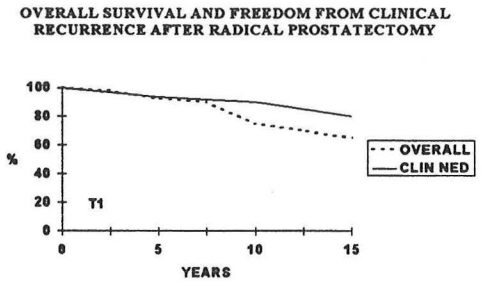

Figure 14 **Ref 73**

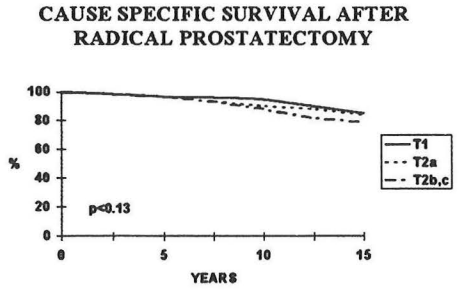

Figure 15 **Ref 73**

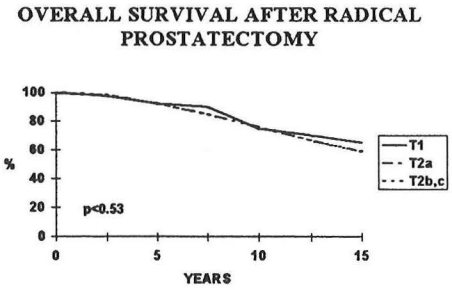

Figure 16 **Ref 73**

at an indolent pace and with reasonably low cancer specific mortality (77). Also, newer radiation therapy techniques, such as conformal radiation and brachytherapy, may improve upon the outcomes with this modality (78,79). The second consideration is that cancer specific mortality is quite low compared to overall mortality (fig 15,16, tbl. 12). This has been interpreted to indicate that, at least, radical prostatectomy has a major therapeutic impact on prostate cancer deaths.

Deferred Treatment: Another critical issue has been raised by critics of PSA based screening for prostate cancer. It has been proposed that, because of the indolent nature of the majority of clinically diagnosed, organ confined tumors, **watchful waiting** (waiting for symptoms to arise and than applying the least toxic, appropriate palliative therapy) is a

reasonable option for management in selected individuals. Several series investigating this approach have been published (80-84). These data have then been compared to results reported for therapy of early prostate cancer using prostatectomy or radiation. Some investigators have concluded that expectant management is a valid option for men with clinically organ confined tumors. Fig 17 is used to illustrate this reasoning. It shows the cause-specific survival of patients with organ confined prostate cancer treated by prostatectomy from the Mayo Clinic series compared to expectant management as compiled in the pooled analysis by Chodak et al (84). The data are displayed by tumor grade. It should be noted that the division by grades is not exactly comparable. The expectant group included grades 8-10 as high grade whereas the surgery group included 7-10. In this example, at 10 years there is little difference in cause specific survival between the two groups with low and intermediate grade tumors. A substantial difference appears to exist for high grade neoplasms. In most series, 5-10% of clinically organ confined tumors are Gleason's score 8-10 and approximately 15-25% are Gleason 7 (56,57,73,84). Adolfson et al. performed a literature review of patients with palpable (clinical stage B) tumors evaluating the cause specific outcomes for groups of patients treated with prostatectomy versus deferred treatment (table 13)(83).

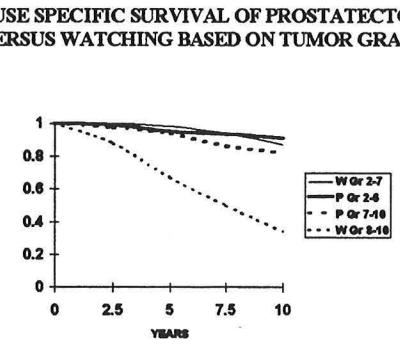

Figure 17 **Ref 73,84**

OUTCOMES FOR CLINICAL STAGE B PROSTATE CANCER MANAGED BY DEFERRED TREATMENT VERSUS RADICAL PROSTATECTOMY

Treatment	Risk per 1000 Patient Years (%)		10 Year Cancer Specific Survival (%)
	Distant Metastases	Death from Cancer	
Deferred	25.1	16.8	84
Prostatectomy	12.6	7	93

Table 13 **Ref 83**

Their analysis calculated means for risk of development of distant metastases, death due to prostate cancer and cause specific survival. The data were weighted for age, numbers of patients per study and tumor grade. They concluded that radical prostatectomy produced a marginal benefit over deferred treatment. Advocates of prostatectomy argue that expectant management

results in unnecessary morbidity and suffering from the eventual local progression of the disease and the development of distant metastases. Supporters of deferred treatment point to the morbidity of radical prostatectomy. (See below). A number of potential biases exist with such comparisons. Median age of patients tends to be 5-10 years higher in watchful waiting protocols. Patients were chosen on differing grounds for each approach, such as co-morbid conditions, patient and physician choice or existing standard of treatment for the institution. Nevertheless decision trees have been constructed for this purpose (85). Analysis of the same data by others has come to contrary conclusions (86).

A further important element in dealing with the impact of radical prostatectomy on the natural history of prostate cancer is the complication rate of the procedure. This is particularly relevant in a screening setting where the standard of therapy for clinically organ confined disease is this operation. Unfortunately, there is no specific answer. It is acknowledged that certain complications, including death, are seen with the surgery. However, the rates vary extremely widely. This is due to several factors. The procedure is very operator dependent. Many published series are from "centers of excellence" (73,75). In some cases, only one surgeon has performed all of the operations (75). The technique itself has changed with time. In some patients, at some centers, a nerve sparing procedure is utilized with lower morbidity (75,95). Patient selection as well as technical expertise becomes paramount. In other settings, the surgery has been performed by lesser experienced individuals such as found in reviews of Medicare patients or broader surveys (7,91,92,96). Table 14 gives the common serious complications and an estimated *range* for the frequency (where available). The incidence refers to those who were continent or potent pre-operatively. These values unquestionably vary widely. In the case of impotence, there is a major dependence on patient age, disease stage and whether nerve sparing surgery is used (75). Thus, discussion of these outcomes is ultimately contingent upon the surgeon that is involved and the techniques used.

COMPLICATIONS OF RADICAL PROSTATECTOMY

	%
Mortality	0.5-2
Impotence	25-72
Urinary Incontinence	5-32
Rectal Injury and/or Colostomy	3
Urethral Stricture	18

Table 14

Only one randomized trial studying the question of prostatectomy versus deferred therapy has been completed. This study concluded that, with 23 years follow-up, no difference between expectant treatment and prostatectomy could be demonstrated (87). Unfortunately, this study was too small (142 subjects) to permit a meaningful comparison.

Recently, another attempt has been launched to study this question in a prospective

randomized trial jointly sponsored by the VA and NCI (88-90). The Prostate Intervention Versus Observation Trial (PIVOT) is presently in the planning and pilot phases. The design of the trial has drawn considerable, often heated, debate (91). The general preliminary design is shown below.

Support: Department of Veterans Affairs and the National Cancer Institute
Investigators: 80+ VA and NCI medical centers
Eligibility: Newly diagnosed prostate cancer
T1/T2NXM0 all histologic grades
Candidate for radical prostatectomy
Less than age 75
Exclusions: Prior prostate cancer therapy (except TURP)
Life expectancy judged less than 10 years
Evidence of non-localized prostate cancer
Recruitment: Patients at the participating centers
Number entered: 2,000 over 3 years
Study Design: Eligible patients will be shown an information and randomization video with discussion with an investigator
Patients agreeing will be randomized to radical prostatectomy or expectant management with palliation for symptomatic or metastatic disease progression
Minimum followup 12 years
Primary endpoint: All cause mortality
Secondary endpoints: Cancer/treatment specific morbidity and mortality
Health status
Predictors of disease specific outcome
Cost-effectiveness

Conclusions: Although claimed by some, a curative outcome from therapy for early prostate cancer has not been conclusively demonstrated. Cause specific survival after prostatectomy for clinically organ confined disease is excellent. Nevertheless, deferred treatment may be a valid option for many patients. The randomized, controlled trial of this question is warranted.

INTERVENTIONAL TREATMENT OF SCREENED CASES SHOULD DECREASE CAUSE SPECIFIC MORTALITY RATES.

This is the crucial point to be documented if mass screening for a malignant disease is to be recommended.

Stage T1c NX M0 cancers: As a consequence of screening men for prostate cancer with the PSA test, a new T designation has been added to the AJCC staging system (see appendix). T1c tumors are cancers detected by needle biopsy that are neither felt on DRE nor imageable. In the literature, these are usually defined as tumors not detected by DRE. Historically, most T1 cancers have been found incidentally at TURP for presumed BPH or at cysto-prostatectomy for bladder cancer. In the majority of instances, these have proven to be insignificant clinically. In the

over 6600 men screened in the multi-institutional study, 11% were found to have an elevated PSA but normal DRE. 24.5% of those biopsied demonstrated prostate cancer (38). Thus, these T1c cancers represented nearly 50% of all of the prevalence malignancies detected. If PSA based screening is to be useful, then the characteristics of these T1c tumors are critical. Investigators at Mayo Clinic and Johns-Hopkins have evaluated the properties of T1c tumors diagnosed at their institutions and compared them to clinical T1a and T2 tumors in their series (58,97). Figure 18 demonstrates the pathologic stage distribution of these three clinical stages following radical prostatectomy. The T1c lesions were intermediate in frequency of pathologic stages between T1a and T2 tumors. In the Johns-Hopkins series, the average Gleason grade was the same as T2 and higher than T1a. Based on tumor size, grade and the number confined to the prostate, they estimated that 16% of the T1c cancers were insignificant. The Mayo clinic investigators estimated that only 9% were insignificant. Their estimate was probably lower because they also took DNA ploidy by flow cytometry into account. With a brief duration of follow-up, the latter group has noted a better recurrence free survival at three years, following prostatectomy, for clinical T1c cancers (89%) than for clinical T2b,c lesions (75%)(Fig 19)(97). These observations *may* indicate that the majority of T1c diagnosed cancers are clinically relevant and that specific therapy produces a more favorable outcome. Although not proven, these data do support the potential benefit of early diagnosis and treatment of a significant proportion of those malignancies detected by PSA screening.

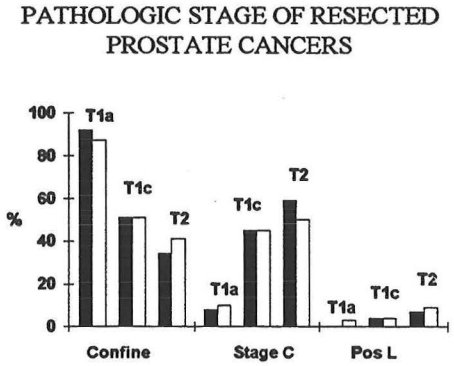

Figure 18 **Ref 58,97**

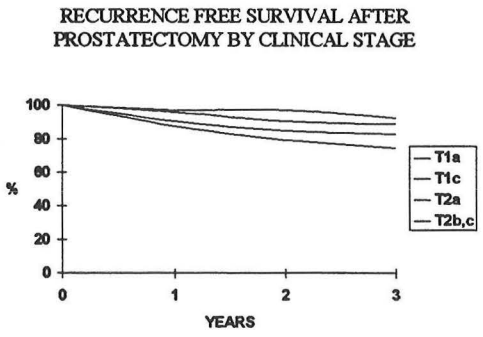

Figure 19 **Ref 97**

However, comparison of a screened group of patients to an historical data base of clinically diagnosed and treated patients is not statistically sound. Certain phenomena and potential biases arise when attempting to evaluate screening in this manner. (8,92) These include:
Stage shift: The pattern at diagnosis shifts to a greater preponderance of earlier stages. This is a

necessary component of successful screening, but not sufficient. **Selection Bias:** The population undergoing screening in the trial does not represent the general population for which the potential for screening exists. Likewise, the screened group and an historical patient population may vary in many important variables. Volunteers for screening studies often possess characteristics not common to the general population (eg. family history, more health consciousness). **Lead Time Bias:** If earlier diagnosis does not effect the natural history, then it merely advances the time of diagnosis and survival appears to be longer. The disease is diagnosed before symptoms arise and therefore the patient lives longer with the knowledge that the disease exists. If intervention earlier doesn't alter the likelihood of dying from the specific disease, then potentially more harm may arise from the detection and treatment. **Length Bias:** Interval cancers, detected because of symptoms between scheduled screens, are usually more aggressive and are associated with worse survival than cancers detected at a screening visit. The slower growing, less dangerous tumors are picked up during a screening visit. **Over-diagnosis:** This is a type of length bias. It comes into play where a large quantity of indolent, non-threatening cancers exist. If the tumor is potentially unimportant, as in the case of many "autopsy" prostate cancers, it is possible that the disease might never become clinically symptomatic during life and death occurs from other causes. Benefit occurs if the tumor is not diagnosed.

For all of these reasons, the most definitive evidence would come from a randomized, controlled screening trial where the primary end-point is cause-specific survival. Recognition of this has led to the design and implementation of a NCI sponsored investigation of this problem (combined with screening for other malignancies as well), the prostate, lung, ovarian and colo-rectal cancer screening trial (PLCO)(7,8). The basic components of the prostate portion are:
Investigators: 10 contracted screening centers plus a coordinating center, laboratory and bio-repository.
Eligibility: Age 60-74 without history of prostate cancer
Exclusions: Not available
Recruitment: Dependent on screening center
Number entered: 74,000
Study Design: Randomized. 37,000 to undergo annual PSA and DRE examinations four times. If either test abnormal/suspicious, prostate biopsy performed.
37,000 to undergo routine medical care.
Annual health status evaluation for both groups.
15 year follow-up from initiation of recruitment and screening
Primary endpoint: cause-specific survival
Treatment: Patients in either arm who have clinically organ confined cancers detected will undergo primary therapeutic intervention (radical prostatectomy or radiation therapy).

At least two other large prospective screening studies are also underway abroad (93,94).

Conclusions: It is not legitimate to evaluate the impact of screening for prostate cancer by comparing outcomes from screened groups of patients to retrospective series of patients with clinically diagnosed disease. Too many potential statistical biases arise. The final answer will depend upon appropriately designed and executed randomized prospective trials. Until this is accomplished, mass screening of asymptomatic males for prostate cancer does not appear to be

justified. Screening, presently, should be performed on an individual basis with the subject being given proper information on the implications of the testing. Attention must be given to patient age, co-morbid conditions, predicted life-expectancy and preferences. If screening is performed, a PSA-DRE based strategy seems best.

Addenda

1. At the recent AUA meeting, several groups presented data on the use of free versus bound PSA to increase PSA specificity. In prostate cancer, free PSA tends to be low relative to bound forms. The data disagreed on cut-off points to recommend biopsy. Use of a threshold for % free PSA reduced negative biopsies 13-40%. In so doing, the number of cancers missed was approximately 10%.

AJCC GUIDELINES FOR STAGING PROSTATE CANCER

TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically inapparent tumor not palpable or 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 PSA)

T2 Tumor confined within the 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 the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than the seminal vesicles
- T4a Tumor invades any of: bladder neck, external sphincter, or rectum
- T4b Tumor invades levator muscles and/or is fixed to the pelvic wall

* Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging is T1c
** Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is T2

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 more than 5 cm in greatest dimension; 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 matastasis
M1 Distant metastasis

Histopathologic Grade (G) G1 Well Differentiated; G2 Moderately differentiated; G3-4 poorly differentiated or undifferentiated

STAGE GROUPING

Stage 0 T1a N0 M0 G1
Stage 1 T1a N0 M0 G2,3-4
T1b N0 M0 Any G
T1c N0 M0 Any G
T1 N0 M0 Any G
Stage II T2 N0 M0 Any G

Stage III T3 N0 M0 Any G
Stage IV T4 N0 M0 Any G
Any T N1 M0 Any G
Any T N2 M0 Any G
Any T N3 M0 Any G
Any T Any N M1 Any G

COMPARISON OF STAGING SYSTEMS
(APPROXIMATE)

TNM	AJCC STAGE	AUA STAGE
T1a N0 M0 G1	0	A1
T1b N0 M0	I	A2
T2a N0 M0	II	B1
T2b,c N0 M0	II	B2
T3a,b N0 Mo	III	C1
T3c N0 M0	III	C2
T4 N0 M0	IV	C2
Any T N1-3 M0	IV	D1
Any T Any N M1	IV	D2

Clinical Stage: Apparent stage at diagnosis following non-surgical staging evaluation

Pathologic stage: Stage determined from specimens removed at exploration or radical prostatectomy

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