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SPECIAL REPORT

Prostate Cancer: A Review of Common Underwriting Problems, Part 2

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This article is Part 2 of a two-part discussion of prostate cancer from an underwriting perspective that covers clinical staging, tissue staging, and follow-up of treated prostate cancer. Prostate biopsy is the diagnostic gold standard. Needle biopsy technique, sensitivity and specificity, and interpretation of findings, including a detailed discussion of Gleason grading, are discussed. Prostate cancer staging using the TNM system and the modified Whitmore-Jewitt system are compared and contrasted. Finally, methods for monitoring post treatment clinical course and the prediction of risk of post treatment recurrence are reviewed.

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BIOPSY AND STAGING: PREDICTING ORGAN-CONFINED DISEASE

Once prostate cancer screening has suggested sufficient suspicion of possible underlying cancer, prostate biopsy may be considered. The difficulties encountered in screening for prostate cancer were reviewed in Part I of this review.[1] Dr. Thomas Stamey, an early advocate for PSA screening, has changed his opinion and is no longer concerned about an elevated PSA until it is in the 7 to 9 ng/mL range. However, Dr. William Catalona disagrees. He performs biopsies on patients with PSA levels as low as 2.5 ng/mL,[2] then biopsy and staging is done. This normally begins with transrectal ultrasonography (TRUS) to guide prostate biopsy.

Prostate biopsy is the gold standard for prostate cancer diagnosis. The site of biopsy may be directed by an abnormality found on a digital rectal examination (DRE), areas of suspicion by TRUS, or by a routine ''schema'' of biopsy of the entire gland. In the standard ultra-sound guided sextant biopsy, a specimen is removed with a biopsy gun from any suspicious areas (by DRE or TRUS) followed by 6 tissue cores from the base, mid-zone, and apical areas of the right and left lobes of the gland. The most common complications of such biopsy include hematospermia (51%), hematuria (23% longer than 3 days), fever (3.5%), and rectal bleeding (1.3%). Fewer than 1% develop urinary retention or require hospitalization (usually for urosepsis).[3]

Increasingly, the sextant biopsy is being re-

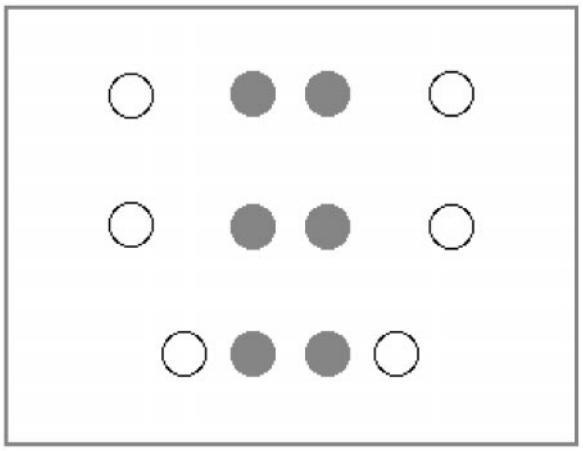

Figure 1. *Prostate core biopsy schema. Coronal prostate plane depicts a 12 core biopsy scheme. Filled circles represent standard sextant sites, while open circles represent additional lateral sites within the gland for extended biopsies. Adapted with permission from: Kantoff P, Taplin M. Overview of the clinical presentation, diagnosis, and staging of prostate cancer. In: UpToDate, Rose BD, ed. UpToDate, Inc. Wellesley, Mass:* UpToDate; *2004. Copyright 2004 UpToDate, Inc. For more information visit www.uptodate.com.*

placed by biopsy schema that sample more areas of the gland, particularly the lateral aspects. In one study of 483 men with serum PSA concentrations of ≥4.0 ng/mL who underwent routine sextant biopsies plus lateral biopsies of the peripheral zone at the base and mid-gland for a total of 10 biopsies, the authors report detecting 96% of the cancers, while traditional sextant biopsy missed 20%. Eliminating the mid-lobar base biopsies, an 8-biopsy scheme maintained a detection rate of 95%.[4] Most recently, a 12-site biopsy scheme to optimize cancer detection has been suggested.[5] (Figure 1) Compared to sextant biopsies, more extensive biopsy schemes are not associated with more abdominal or rectal pain, although hematochezia and hematospermia may be more frequent.[6]

Up to one fourth of prostate cancers are missed on initial biopsy.[7] Especially when suspicion warrants it, a repeat biopsy is needed. In one report, cancer was detected in 83 of 820 (10%) second biopsies, and third and fourth biopsies yielded a cancer diagnosis in 4% and 5% of cases, respectively.[8] At the other end of the spectrum is the occasional problem of over-diagnosis on needle-core biopsy. Prostatectomy done when the needle biopsy reveals minute foci of tumor (3 mm or less) is associated with tumor volume of 0.5 mL or less 30% of the time. Some question the need for surgery for such a small volume of tumor.

If one or multiple biopsies done for elevated PSA have consistently negative results, a new area of investigation is molecular assays for urinary detection of prostate cancer. Promoter hypermethylation of the glutathione S-transferase (GST1) gene is one of the earliest molecular changes in prostate cancer and may be detected after prostatic massage. In a study of 45 men with BPH and 40 men with prostate cancer, the overall sensitivity and specificity for detection of cancer were 73% and 98%, respectively.[9] Telomerase in urine has also been used as a marker for prostate cancer,[10] with 58% sensitivity and 100% specificity. The advantage of these tests is their high specificity, thereby permitting identification of men with a high serum PSA due to BPH and avoiding additional or continuing prostate biopsies.

PROSTATIC INTRAEPITHELIAL NEOPLASIA

Prostatic intraepithelial neoplasia (PIN) is a precursor of invasive carcinoma and a marker for concurrent adjacent carcinoma.[11] PIN is categorized as low grade or high grade. High-grade PIN has a high predictive value as a marker for adenocarcinoma, necessitating close follow-up for concurrent or subsequent invasive cancer. In one recent study of men with atypia and high-grade PIN on biopsy, 51% had confirmed cancer on re-biopsy.[12] Low-grade PIN first emerges in men as early as the third decade of life, and the incidence of PIN increases with age and is very common in the elderly. PIN may cause increased levels of serum PSA, but the major mortality risk of PIN is related to adjacent or subsequent invasive carcinoma. Autopsy studies indicate PIN preceded carcinoma by 10 years or more.

GRADE OF TUMOR (GLEASON)

With the Gleason histological scoring system, tumors are graded from 1 to 5 based upon the degree of glandular differentiation and structural architecture. Grade 1 represents the most well differentiated appearance, and grade 5 represents the most poorly differentiated appearance. A primary score and a secondary score are reported, and these are combined to form the Gleason score. If a biopsy consists of predominantly grade 3 and secondarily grade 4 disease, the Gleason score is then 3 + 4 = 7.[13] Combined scores of 2, 3 and 4 usually represent well-differentiated or low-grade cancers. Scores of 5, 6 and 7 represent moderately differentiated cancers, and scores of 8, 9 or 10 represent poorly differentiated (high-grade) cancers. (Although some call Gleason 7 moderately poorly differentiated—see following discussion.)

From a study of 15-year mortality in conservatively-treated men ages 55–74 years at diagnosis, the results include the following:[14]

- Gleason score of 2 to 4: 4% to 7% risk of death
- Gleason score of 5: 6% to 11% risk of death
- Gleason score of 6: 18% to 30% risk of death
- Gleason score of 7: 42% to 70% risk of death
- Gleason score of 8–10: 60% to 87% risk of death

According to personal communication with Dr. Gleason, he believes that all Gleason 5/5 = 10 cancers are already associated with metastases.

A 1999 study noted that ''no patient with a Gleason tumor score of less than 6 developed metastatic disease, whereas only 40% of patients with a Gleason tumor score of between 8 and 10 were free of metastases after 5 years.''[15] Gleason scores from needle biopsies are not always representative of the Gleason score of the aggregate tumor[16,17] and the likelihood of upstaging (see section on Staging of Prostate Cancer) at surgery is directly related to the Gleason score of the tumor.

Table 1. Quick Comparison of the Whitmore-Jewett and TNM Classifications

Low-risk	Intermediate Risk	High Risk
T1a = A1		T2c = B3
T1b = A2	T2b = B2	T3a = C1
T1c = B0		T3b,c and T4 = C2
T2a = B1		N+ = D1
		M+ = D2

Although Gleason stage 7 has classically been included in the ''moderately-differentiated'' grouping, the seriousness of Gleason stage 7 is causing many pathologists, urologists (and insurance physicians) to group this with the higher-grade 8 to 10 grouping. Recent data suggests that the percentage of Gleason's pattern 4 or 5 in the specimen is the prime determinant of outcome,[18] suggesting that ''all Gleason grade 7s are not equal'': a Gleason score of 3 + 4 = 7 is likely of less prognostic significance than Gleason grade 7s comprised of 4 + 3 = 7 and/or 5 + 2 = 7. Litwin states, ''Tumors with Gleason scores of 5 to 7 cannot be lumped together as they often are. While tumors with a Gleason score of 5 act like their lower-grade cousins, tumors with a Gleason score of 6 cause death in 18% to 30% of men . . . tumors with Gleason score of 7 are still more ominous . . . fully 40% of men with tumors with a Gleason score of 7 will die of prostate cancer if their tumors are left untreated.''[19] Finally, the likelihood of upstaging at surgery rises sharply with a Gleason score of $\geq$7.[20,21]

TNM STAGING

Although tumor-node-metastasis (TNM) system is the most common method of staging prostate cancer, the American Urologic Association (modified Whitmore-Jewett) system is still used. The two systems are roughly, but not completely, comparable.[22–24] (Table 1).

Patients are generally assigned a clinical T stage, or ''c'' stage, and a pathologic T stage, or ''p'' stage. The ''c'' stage is determined by

Table 2. Staging of Prostate Cancer by 2002 AJCC Staging System

Clinical Tumor (cT) Stage	Substage
Stage cT1–Clinically unapparent tumor neither 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 PSA)
Stage cT2*–Tumor confined within the prostate	T2a–Tumor involves half of one lobe or less
	T2b–Tumor involves more than half of one lobe but not both lobes
	T2c–Tumor involving both lobes
Stage cT3†–Tumor extends through the prostate capsule	T3a–Extracapsular extension (unilateral or bilateral)
	T3b–Tumor invades the seminal vesicle(s)
Stage cT4–Tumor is fixed or invades structures other than seminal vesicle(s): bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	
Pathologic Tumor (pT) Stage	
Stage pT2–Organ confined	pT2a–Unilateral
	pT2b–Bilateral
Stage pT3–Extraprostatic extension	pT3a–Extraprostatic extension
	pT3b–Seminal vesicle invasion
Stage pT4–Invasion of bladder, rectum	
Regional lymph nodes	NX–Regional nodes not assessed
	NO–No regional lymph node metastasis
	N1–Metastasis in regional lymph nodes
Distant metastasis	MO–No distant metastasis
	M1–Distant metastases present

* Tumor found in one or both lobes by needle biopsy but not palpable or reliably visable by imaging is classified T1c.

† Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2 disease.

DRE, while the ''p'' stage is determined after a pathologist has evaluated a radical prostatectomy specimen.

When interpreting the results of published studies, it is important to note whether clinical or pathologic stage is used, since there may be discrepancies. For example, a patient who has a palpable nodule on the left side of the prostate gland by DRE but who has cancer in both lobes on biopsy is still given the clinical stage of T2a.

The confusion regarding the sub-categories in T2 (Whitmore-Jewett B) can usually be clarified by reading the actual pathology report to assess the extent of the tumor (ie, is it in one lobe or both, and is the cancer limited or extensive?). Note that a tumor invading the capsule but not spreading *through* the capsule is considered T2 (B2) rather than T3 (C).[25] Some authorities feel that when there is only a small penetration (eg, 0.5 cm) of the capsule this often does not adversely affect prognosis.[26] However, it may be difficult to determine the extent of capsule penetration.

Clinical staging often underestimates the extent of tumor found at surgery. In a combined series evaluating over 8000 men who underwent radical prostatectomy for disease at clinical stage T1 and T2, the cancer was histologically confined to the prostate at the

time of surgery in only 52%.[27–33] Recent studies, however, suggest that the likelihood of finding organ confined disease based on clinical stage has increased substantially during the PSA era as a result of widespread screening (finding earlier cancers), which has resulted in a downward migration in pathological stage.[34] In a contemporary series of 1313 men undergoing radical prostatectomy[35] (53% of cases occurring after 1995), clinical understaging only occurred in 24% of cases (vs the 52% reported earlier).

PERINEURAL INVASION

The available data concerning the impact of perineural invasion (PNI) on prognosis after definitive therapy are inconclusive. In one series, the likelihood of a positive margin was 25% in men with PNI vs 17% with no PNI on the biopsy specimen.[36] In two large contemporary series of men with clinically localized disease, one using radiation therapy and the other surgery, the presence of PNI in the biopsy specimen was an independent predictor of biochemical relapse-free survival in men with low-risk disease (defined as serum PSA <10 ng/mL, Gleason score ≤ 6, and clinical T1c or T2a disease). However, the presence of PNI provided no additional prognostic value for men with intermediate or high-risk disease.[36,37] In contrast, no adverse influence of perineural invasion on outcome was found in a series of 78 men with PNI on pre-prostatectomy biopsy who then underwent radical prostatectomy.[38] With a mean follow-up between 7 and 8 years, there was no significant difference in biochemical relapse-free survival between the two groups.

ENDORECTAL COIL MRI

The use of endorectal coil MRI may improve the preoperative detection of seminal vesicle invasion or extracapsular extension, thereby excluding patients with these adverse features from radical prostatectomy. In one series of patients with clinical stage T1/T2 disease, serum PSA 10 to 20 ng/mL, biopsy Gleason score of 7 or less, and at least 50% of biopsy samples from sextant sampling positive, the sensitivity of endorectal coil MRI was 65%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 79%.[39]

FLOW CYTOMETRY

As is commonly seen with most neoplasms, abnormal DNA content in prostate cancer predicts more aggressive behavior. Flow cytometry in prostate cancer may be described as diploid (95% 5-year survival), tetraploid (70% 5-year survival), or aneuploid (25% 5-year survival). In a Mayo Clinic 10-year follow-up study of men with prostate cancer with positive lymph node spread, there were no prostate cancer deaths in the DNA diploid group. In those studied longer, some diploid patients survived up to 20 years if treated.[40] Nevertheless, many researchers now believe that DNA ploidy analysis adds little significant information beyond the Gleason grade.[31]

PERCENTAGE OF POSITIVE BIOPSIES

An estimate of tumor volume in the prostate needle biopsy can add clinically significant information to other factors. Those factors include preoperative serum PSA, biopsy Gleason score, and AJCC clinical T stage in the selection of patients to undergo radical prostatectomy or radiation therapy. The generic term ''percentage of positive biopsies'' is used when biopsy tumor volume is quantified by the maximal percentage of a core involved with cancer, the percentage of cores that are positive, or the pathologist's estimate of percentage of biopsy tissue containing cancer overall. The influence of prostate biopsy tumor volume on outcome was illustrated in a report of 960 surgically treated men. In this report, 80% of those in the intermediate risk group (1992 AJCC clinical stage T2b, biopsy Gleason 7, or preoperative serum PSA 10–20 ng/mL) could be classified into two separate risk groups based upon the fraction of pros-

tate biopsies that were found to contain cancer.[41] Patients with >50% positive biopsies had an 11% likelihood of PSA stability at 4 years. Patients with <34% positive biopsies had an 86% likelihood of PSA stability at 4 years. In contrast, the percentages of positive biopsies provided no additional prognostic value in patients at low risk for recurrence (stage T1c or T2a, PSA ≤10 ng/mL, and Gleason score of ≤6).

A subsequent report revealed that among men at low risk of recurrence, those with >50% positive biopsies were significantly more likely to be pathologically upgraded at the time of surgery from Gleason 1–7 tumors than those with fewer than 50% positive samples (59% vs 26%).[42]

CANCER VOLUME

Another refinement in predicting the likelihood of organ-confined disease in patients with clinically localized prostate cancer is the calculated cancer volume. The calculated cancer volume takes into consideration the prostate gland volume (as determined by TRUS), serum PSA, and the biopsy Gleason score.[43] In a series of 1773 men with clinically localized prostate cancer undergoing either radical prostatectomy or conformal radiation therapy at two different institutions, a calculated volume greater than 4.0 cm^3 identified patients with a shorter time to PSA failure than was predicted by their T stage (clinical T1c or T2 for patients treated by radiation, and pathological T2 stage for those undergoing radical prostatectomy).

HIGH-RESOLUTION MRI WITH MAGNETIC NANOPARTICLES

Massachusetts General Hospital and Harvard Medical School researchers have recently published data[44] on the use of highly lymphotropic superparamagnetic nanoparticles in conjunction with high-resolution resonance imaging. This technique revealed small nodal metastases that are missed by regular pre-operative MRI screening. These nanoparticles have a monocrystalline superparamagnetic iron oxide core containing densely packed dextrans and are avidly taken up by tumor-stimulated macrophages within lymph nodes. They studied 80 patients with presurgical clinical stage T1, T2 or T3 prostate cancer with lymph node dissection. Of 334 lymph nodes that were resected or biopsied, 63 nodes (19%) from 33 patients (41% of the total) had histopathologically detected metastases. Of these 63 nodes, 45 (71%) did not fulfill the usual imaging criteria for malignancy. MRI with lymphotropic superparamagnetic nanoparticles correctly identified all patients with nodal metastases. A node-by-node analysis had a significantly higher sensitivity than conventional MRI (90.5% vs 35.4%, $p<0.001$) or nomograms.

COMBINED MODALITY STAGING AND DEVELOPMENT OF PREDICTIVE MODELS

Compared to any individual factor, the use of combinations of clinical and pathologic factors (pretreatment serum PSA, biopsy Gleason score, and AJCC-defined T stage) allow for more reliable prediction of pathologic stage and treatment outcome. In assessing treatment outcome, cause-specific survival is the gold standard. However, clinical databases do not contain enough long-term follow-up data to adequately evaluate this endpoint. As a result, most studies evaluating pretreatment predictive factors have utilized the time to PSA failure (ie, time to a rise in PSA signaling recurrent and/or metastatic disease) as an intermediate end point.

When using serum PSA as an intermediate end point, the following caveats should be kept in mind:

- A rise in serum PSA may predate the development of metastatic disease by several years. In one series of 304 men who had undergone radical prostatectomy for clinically localized disease and were followed up with every 3-month serum PSA measurements, the median time to develop-

ment of distant metastases was 8 years after the first rise in PSA level.[45]

- Biochemical failure may not be an accurate predictor for overall survival following either radical or external beam radiation. In one report of 1132 surgically treated men in whom biochemical failure developed in 19%, the 10-year survival rates for patients with and without biochemical failure were similar (88% vs 93%).[46]

Several predictive models (Partin model,[47] D'Amico model[48]) have been devised to assign men with prostate cancer who have completed evaluation into an appropriate grouping for proposed therapy (also for an insurance underwriting estimate of expected survival post therapy).

For instance, a series using the Partin model provided long-term follow-up of 2127 men with clinically localized prostate cancer who underwent radical prostatectomy. The 10-year PSA failure-free survival rates for men in the low-risk (T1c or T2a, *and* PSA <10 ng/mL, *and* Gleason score of ≤6) was 83%. Those in the intermediate-risk group (clinical stage T2b, *or* PSA between 10 and 20 ng/mL, or biopsy Gleason score of 7) had a 10-year PSA failure-free survival rate of 46%; and those initially in the high-risk group (T2c disease or PSA >20 ng/mL or Gleason score of ≥8) had a 10-year PSA failure-free survival rate of 29%.[49]

In an initial report of 977 men with palpable (T2) or PSA-detected (T1c) prostate cancer who underwent D'Amino model staging, the following patterns were found to predict early (within 2 years) biochemical failure and subsequent disease progression:

- Endorectal MRI-predicted T3 disease, and ≥3 of 6 cores positive for Gleason score of ≥6, and serum PSA between 10–20 ng/mL.
- Endorectal MRI-predicted T3 disease, and ≥3 of 6 cores positive, and any Gleason score when the serum PSA >20 ng/mL.
- Endorectal MRI-predicted T2 disease, and ≥3 of 6 cores positive for a Gleason score ≥8 and serum PSA >20 ng/mL.[48]

CONCLUSION

Both the frequency of occurrence of prostate cancer in men and its propensity for causing premature morbidity and mortality requires insurance physicians to have a good understanding of those factors that lead to accurate underwriting assessment. Such knowledge begins with understanding the role DRE and measurements of serum prostate-specific antigen (serum PSA) play in screening for prostatic carcinoma. This paper confirms both the strengths and the weaknesses of these tests in screening for cancer of the prostate.

A major unexpected finding in our review was that DRE is currently not recommended as part of a routine health exam. The USPSTF, ACP, the British Health Service and others consider a screen for prostate cancer and serum PSA measurements done for prostate cancer screening ''inadvisable'' as part of a well-man complete physical exam and health assessment.[1] That is, the weight of medical evidence suggests that performing these tests is more likely to cause harm due to inaccuracies, extra testing, and perhaps unneeded therapy, than to help by providing early intervention and cure, or treatment and control. This recommendation is so counter-intuitive that it's been difficult for us to accept. However, we felt these new recommendations need to be understood by clinical and insurance physicians alike. We have also pointed out that justification for ordering and using such data by insurance companies for underwriting may be justified on financial grounds that are not considered or thought relevant by medical academicians.

DRE and measurement of serum PSA are not only used for screening for prostate cancer, but they also have been proven to be powerful predictors of treatment success or failure. There is really no ''normal'' serum PSA, but rather the lower the serum PSA concentration, the less-likely the screened person has cancer and/or resectable disease. Although serum PSA of <4.0 ng/mL is usually considered ''normal,'' in fact, serum PSA in

the 1 to 2.4 ng/mL range carries significantly less risk than serum PSA in the 2.5 to 4.0 ng/mL range.

A unique problem in prostate cancer is that many men may have minute amounts (estimated to be volumes <0.5 cm^3) of what appears to be very benign tumor. No good strategy exists for defining this population that may in fact be harmed, rather than helped, by discovery and therapy of this clinically benign cancer variant.

Of the various strategies devised to improve screening and analysis of detected prostatic cancer, the use of the ratio of free vs total PSA and the measurement of complexed PSA seem to hold the most promise.

Central to correct underwriting of prostate cancer is the prognostic role of the Gleason score reported on prostate biopsy. Formerly Gleason score 7 was lumped with Gleason scores of 5 and 6 as being ''intermediate prostate cancer.'' However, it is now recognized that Gleason score of 7, especially if the predominant tissue is Gleason score 4 or 5, should be grouped with the more ominous high-grade Gleason 8–10 group.

Finally, this paper has reviewed why ''chemical-free survival'' (ie, no recurrence or rise in serum PSA) is used rather than actual deaths in assessing cancer interventions. We reviewed why this endpoint may be a poorer reflection of disease management and prognosis than would be ideal in underwriting applicants for life insurance and disability.

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