There is strong evidence from longitudinal cohort studies of men with both treated and untreated Gleason 6 prostate cancer to suggest that Gleason 6 disease, when not associated with higher-grade cancer, virtually never demonstrates the ability to metastasize and thus represents an indolent entity that does not require treatment.

**Source:**

ABSTRACT: Autopsy studies of men without known prostate cancer suggest that a substantial reservoir of prostate cancer that does not cause symptoms or death exists within the population. The majority of these cancers are Gleason 6 tumors and are frequently detected by prostate-specific antigen-based prostate cancer screening. There is strong evidence from longitudinal cohort studies of men with both treated and untreated Gleason 6 prostate cancer to suggest that Gleason 6 disease, when not associated with higher-grade cancer, virtually never demonstrates the ability to metastasize and thus represents an indolent entity that does not require treatment. Whether Gleason 6 has a propensity to progress to higher-grade cancer is still under investigation. Because the term “cancer” has historically been used to represent a disease state that leads to progressive illness that is uniformly fatal without treatment, we believe Gleason 6 disease should not be labeled with this term. Our challenge now is to develop the technology to differentiate true Gleason 6 disease from the higher grades of dysplasia with which it can be associated.

**Introduction**

The first known recorded descriptions of malignant tumors are found in the Edwin Smith Papyrus, written in Egypt in approximately 3,000 BC.[1] The word “cancer” did not appear until approximately 2.5 millennia later, when Hippocrates invoked the Greek word *karkinos*, or “crab,” to describe tumors he observed, possibly because of their propensity to insinuate into surrounding tissues and adhere tenaciously, as if by the use of claws. Roman physicians continued to liken cancers to the crab and translated the Greek term into the Latin word *cancer*. For the subsequent 2,000 years, the clinical entity of cancer remained a disease that was recognized primarily in its locally advanced or metastatic stage, when it was almost uniformly fatal.

The rapid advances in diagnostic technology of the later part of the 20th century meant that for the first time the detection of cancer was possible when the disease was confined to the organ of origin and amenable to cure. In some cases, technology enabled abnormalities at the subclinical level to become detectable years before recognition of the clinical entity of cancer. The benefits of screening and early intervention have been consistently demonstrated in certain cancers, such as cervical and breast cancer.[2,3] For other malignancies, including adenocarcinoma of the prostate, the risk/benefit ratio is controversial and more difficult to quantify. It is now widely recognized that a substantial proportion of screening-detected prostate cancers are unlikely ever to become clinical cancers during the lifetime of the patient. This phenomenon, the detection of a condition that would not go on to cause symptoms or death, is referred to as “overdiagnosis.”[4]

The current paradigm for screening and detection of prostate cancer has resulted in overdiagnosis for several reasons. First, the instrument for prostate cancer screening, the prostate-specific antigen (PSA) blood test, uses a nonspecific serum marker that is elevated not only in prostate cancer but also in a host of benign prostate conditions, resulting in substantial false-positive results.[5] Second, the confirmatory test, the prostate biopsy, is performed by taking random but systematically directed biopsies of the prostate in men with an elevated PSA level. Random biopsy risks both the detection of indolent cancers and the failure to diagnose clinically significant cancers.[6] Because it is known from autopsy series that between 30% and 40% of prostate glands in men > 50 years of
For more than 5,000 years, the clinical entity of cancer has implied a process of invasion, destruction, metastasis, and death. Assigning a diagnosis of cancer to a patient instills intense fear of an almost inevitable demise unless aggressive attempts are made to eradicate the disease. But today our current diagnostic armamentarium has given us the ability to aggressively identify and treat pathologic cancers, the majority of which are not likely to cause harm. It is time to reappraise whether these indolent abnormalities should be labeled with the term “cancer.” Concern about overdiagnosis has become especially focused on Gleason 6 disease, given multiple lines of evidence suggesting that the majority of Gleason 6 disease, while demonstrating the ability to invade pathologically, does not appear to have the propensity to invade clinically. If this is the case, is Gleason 6 disease truly a cancer?

Gleason Grading System

The purpose of staging and grading cancers is to provide insights regarding the extent and aggressiveness of the malignant process. Since its initial description in 1966, the Gleason scoring system has become the most widely accepted system for the pathologic grading of prostate adenocarcinomas, largely because of its consistent reproducibility and robust ability to independently predict disease outcomes.[13-15] This system assigns a grade to the tumor based on the tumor architecture viewed under relatively low power (4–10×). The more the glandular architecture deviates from normal, the higher the Gleason grade. A Gleason score takes into account that prostate cancer is often multifocal and that there are different Gleason patterns even within a single index lesion. The most predominant (primary) and second most predominant (secondary) patterns of tumor glandular architecture are identified, and each is assigned a grade of 1 to 5. The Gleason sum, or score, is obtained by adding these primary and secondary Gleason grades together. Since its initial description, the Gleason system has undergone several modifications and clarifications. The most recent modification occurred in 2005 and established the contemporary system, known as the 2005 International Society of Urological Pathology (ISUP) modified Gleason system.[16] Several changes from the previous version should be noted. In the modified 2005 system, Gleason patterns of 1 or 2 are rarely, if ever, diagnosed, particularly for needle-biopsy specimens. The reasons for this include low interobserver agreement for Gleason patterns 1/2 even among uropathologists, poor correlation between needle-biopsy and radical prostatectomy specimens for these grades, and fear that the diagnosis of these well-differentiated patterns may lead to overtreatment. In addition, in the modified 2005 system the majority of cribriform glands, as well as ill-defined glands with poorly formed lumina, have been removed from the pattern 3 category and are now considered higher-grade and are thus assigned to pattern 4, both increasing the stringency for making the diagnosis of purely pattern 3 and expanding the pattern 4 category. These subtle modifications to the Gleason system have resulted in two noteworthy changes. First, the virtual elimination of patterns 1 and 2 narrows the Gleason score from a 9-point scale (2–10) to a 5-point scale (6–10). Second, and more importantly, the increased stringency for the diagnosis of purely pattern 3 disease means that men who receive a diagnosis of Gleason 3+3 disease using the modified 2005 system are likely to have less aggressive tumors than men who received a diagnosis of Gleason 6 disease in years past, and as such are likely to have improved oncologic outcomes.[17]
prevalence of undiagnosed prostate cancer in the population that ranges from approximately 18% to 40%. Of these incidentally detected cancers, at least 80% were exclusively Gleason pattern 3 disease. Specimens from cystoprostatectomy performed for bladder cancer exhibit a somewhat higher rate of malignancy overall, ranging between 41% and 54%, but the prevalence of high-grade elements is also quite low, with > 70% demonstrating only Gleason pattern 3. Taken together, these studies reveal the presence of a large reservoir of prostate cancers, the majority of which are Gleason 6, which exist in the population and do not cause clinical symptoms or death. Many of these prostate cancers could potentially be diagnosed by PSA screening and random systematic biopsy, suggesting that a substantial proportion of Gleason 6 disease detected by PSA screening represents disease that may never lead to metastasis or death.

How Reliable Is Our Detection of Gleason 6 Disease?

Before the PSA screening era began in the late 1980s, prostate cancer was usually diagnosed by directing a biopsy needle into a nodule detected at the time of a digital rectal examination. In most cases, the nodule occupied a significant proportion of the gland. Often, gross extracapsular disease was evident at the time of diagnosis. Low-grade cancers were rarely diagnosed unless they were incidental findings at the time of transurethral prostatectomy for benign disease.

The detection of prostate cancer in the PSA era requires a random biopsy technique because transrectal ultrasonography (TRUS) does not reliably identify the site of clinically significant disease. Therefore, many Gleason 6 cancers identified on biopsy coexist with higher-grade disease missed by random biopsy. Mufarrij et al.[21] examined the prostates of 205 and 771 men who met the Epstein[22] or Klotz[23] criteria, respectively, for active surveillance and who underwent radical prostatectomy. By definition, all of these men had Gleason 6 cancers on prostate biopsy. Between 45.9% and 47.2% had Gleason grade 4/5 disease, and 7.8% to 10.9% had evidence of extracapsular extension. The 5-year biochemical-disease–free survival was estimated to be 83.2% to 92.9% despite curative intervention. Others have confirmed the unreliability of Gleason grading attributable to random biopsy,[6] which remains an essential limitation in assigning men to active surveillance. It is therefore almost impossible to define the natural history of diagnosed Gleason 6 disease, since almost one-half of these cases are truly Gleason 7 or higher disease at the time of diagnosis. Thus, it is unclear whether disease progression in men presumed to have Gleason 6 disease is due to progression of the Gleason 6 elements or represents a consequence of coexisting higher-risk disease.

Does Untreated Clinical Gleason 6 Disease Cause Symptoms or Death?

Several studies that examined the natural history of untreated prostate cancer diagnosed in the pre–PSA screening era have suggested that men with Gleason 6 cancers are at risk for prostate cancer–specific mortality beyond 10 years of follow-up.[24,25] The majority of the Gleason 6 disease was T1a/b disease, which was identified at the time of transurethral resection of the prostate (TURP) for benign disease. Today, it is extremely rare to diagnose T1a/b disease because fewer TURPs are performed and those undergoing TURP have been prescreened with PSA testing. The results of the natural history studies in the PSA screening era are also problematic because many of the cases were likely misclassified at the outset because of the aforementioned limitations attributable to the random-systematic tissue sampling guided by TRUS. Albertsen et al.[24] estimated that men who received a diagnosis of Gleason 6 disease in the pre-PSA era and were managed conservatively had approximately a 30% (23%-37%) prostate cancer mortality rate after 20 years, but this study is potentially flawed and may not be applicable to contemporary cohorts for multiple reasons. First, no PSA measurement was available at the time of diagnosis. Second, the majority of cases were detected following TURP, which does not sample the peripheral zone, where most cancers reside. Third, a substantial number of patients did not undergo a metastatic evaluation at the time of diagnosis. Bone scans were performed in only 30% of patients, and confirmation of a normal serum acid phosphatase level was obtained in only 53% of patients. Thirty-year follow-up data were recently published on a cohort of 223 patients who received a diagnosis in the pre-PSA era and who were all managed conservatively.[25] This study included 65 patients with Gleason 3–6 disease, and 70 patients classified as low risk based on the World Health Organization grading system (an alternative grading scheme to the Gleason system). Metastatic disease developed in 9 of these 70 low-risk patients, 8 of whom died of prostate cancer during the 30-year period. The progression to metastatic disease and death from prostate cancer per 1,000 person-years in this series were 14.1 and 12.4, respectively. This translates to 1,000 men with...
Gleason 6 disease followed for 10 years, of whom 14 would progress to metastatic disease and 12 would progress to death. Even these favorable results are likely an overestimate of the risk of men who receive a diagnosis of Gleason 6 disease in the current era because the risk stratification of men in this study was based on TURP specimens and fine-needle aspiration. TRUS-guided biopsy and PSA measurement were not available at the time of their initial stratification. It is likely that misclassification took place; thus, many of these men probably had some component of higher-grade disease.

Additional insights about the natural history of Gleason 6 disease can be derived from long-term follow-up of men who select active surveillance. Interpretation of these studies requires the recognition of the significant rate of undergrading in these series due to the current limitations in risk stratification. The majority of active surveillance protocols include only patients with low-volume Gleason 6 disease; thus, disease progression in these cohorts may be a surrogate for the natural history of untreated Gleason 6 disease. These studies have consistently demonstrated a rate of progression on subsequent biopsy ranging from 12% to 38%. However, these data are somewhat difficult to interpret. While they may represent progression of disease over time, the well-documented propensity of TRUS-guided biopsy to undergrade tumors means that a substantial proportion of this upgrading is likely attributable to sampling error of the initial biopsy, meaning that the higher-grade disease was present but missed at the time of initial biopsy. Despite this, true grade progression, and not simply upgrading on subsequent biopsy due to sampling error, does appear to take place in certain cases. Sheridan et al evaluated 241 men with Gleason 6 disease on active surveillance, of whom 45 (18.7%) showed an increase in grade on subsequent biopsy. Of these 45 men, 24 (53%) progressed within 24 months, suggesting that these men likely had higher-grade disease from the outset. The additional 21 men who progressed did so after 2 years and after multiple prior biopsies, which points to one of three possibilities. First, these foci may represent Gleason 6 disease that had progressed in grade to Gleason 7. Second, and equally plausible, independent foci of Gleason 7 may have arisen de novo. Third, it is possible that preexisting small foci of Gleason 7 grew to the extent they became detectable by the random biopsy technique only after several years of follow-up and repeat biopsy.

With reported median follow-up ranging from 22 to 82 months, current active surveillance cohorts remain immature at this time, and longer follow-up will be necessary to draw definitive conclusions. Thus far, cancer-specific survival among these cohorts has been > 97%, and there are no data to suggest inferior outcomes after delayed radical therapy, as compared with immediate therapy.

**Does Gleason 6 Disease Have Metastatic Potential?**

Evidence from multiple cohorts with significant long-term follow-up strongly suggests that Gleason 6 disease, at least at the time of treatment, does not demonstrate the biologic capacity for metastatic spread. A single-surgeon series from New York University demonstrated that of 857 men who underwent radical prostatectomy for true pathologic Gleason 6 disease, 16 (1.9%) had a significant biochemical recurrence (BCR). Of these, all 16 men underwent salvage radiation therapy and 14 had durable PSA responses, indicating that their relapse was caused by residual local disease only. Of the 2 men who did not respond, which suggests systemic disease, a review of their pathology demonstrated Gleason pattern 4 elements in both. These data indicate that although Gleason 6 disease; thus, disease progression in these cohorts may be a surrogate for the natural history of untreated Gleason 6 disease. These studies have consistently demonstrated a rate of progression on subsequent biopsy ranging from 12% to 38%. However, these data are somewhat difficult to interpret. While they may represent progression of disease over time, the well-documented propensity of TRUS-guided biopsy to undergrade tumors means that a substantial proportion of this upgrading is likely attributable to sampling error of the initial biopsy, meaning that the higher-grade disease was present but missed at the time of initial biopsy. Despite this, true grade progression, and not simply upgrading on subsequent biopsy due to sampling error, does appear to take place in certain cases. Sheridan et al evaluated 241 men with Gleason 6 disease on active surveillance, of whom 45 (18.7%) showed an increase in grade on subsequent biopsy. Of these 45 men, 24 (53%) progressed within 24 months, suggesting that these men likely had higher-grade disease from the outset. The additional 21 men who progressed did so after 2 years and after multiple prior biopsies, which points to one of three possibilities. First, these foci may represent Gleason 6 disease that had progressed in grade to Gleason 7. Second, and equally plausible, independent foci of Gleason 7 may have arisen de novo. Third, it is possible that preexisting small foci of Gleason 7 grew to the extent they became detectable by the random biopsy technique only after several years of follow-up and repeat biopsy.

In a related study, Miyamoto et al reanalyzed 2,551 cases of Gleason 6 organ-confined tumors in the Hopkins (Walsh) series and identified only 38 (1.5%) cases of BCR. Of the 38 cases in which a BCR developed, 27 (71%) were found on rereview to have a higher stage or grade than originally coded. Thus, a BCR developed in only 11 of 2,551 (0.4%) cases with true organ-confined Gleason 6 tumors. The same group combined data from four institutional radical prostatectomy databases and identified the rare instances (22 of 14,123 cases) in which patients with pathologic Gleason 6 tumors had lymph node metastases. A review of the final pathology in these cases demonstrated that there had been undergrading in every case; thus, in no case had a true pathologic Gleason 6 tumor metastasized to the lymph nodes at the time of the patient’s radical prostatectomy.

Overall, the data are quite convincing that pathologic Gleason 6 disease (with the score based on the 2005 ISUP modified Gleason system) poses virtually no risk of metastatic disease. The challenges for today’s practitioner are how to identify those men who truly have pathologic Gleason 6 disease, without higher-grade elements, and how to be confident that they will not later receive a diagnosis of higher-grade disease.
Can Gleason 6 Progress to Higher-Grade Disease? Epidemiologic Evidence

Currently available data regarding the potential for progression of Gleason 6 disease during its untreated natural history are conflicting. Epidemiologic evidence exists to support the concept of a nonprogressive and benign indolent course as well as a progressive course in which more aggressive disease can develop from initially low-risk lesions. One might then hypothesize that if multiple stepwise genetic events are required to transform low-grade nonclinical tumors into more aggressive disease, the total number of low-grade cancer cells present in a gland may affect the patient’s likelihood of developing aggressive disease. Whittmore et al.[33] evaluated this question and hypothesized that the incidence of high-grade disease would be proportional to the volume of low-grade cancer in the prostate, thus suggesting that lower-grade dysplasia is at risk for progression to higher-grade disease. Using autopsy pathology data to estimate low-grade cancer volume and Surveillance, Epidemiology, and End Results (SEER) Program prostate cancer incidence to infer high-grade clinical cancer rates, the researchers generated curves comparing latent tumor volume and high-grade cancer incidence. They found that on average, each milliliter of low-grade tumor at any age will have yielded 0.024 high-grade cancers per year after approximately 7 years. In more intuitive terms, in a hypothetical group of 100 men who all have a 1-mL focus of low-grade tumor in their prostate, an average of 2.4 will have presented with aggressive disease by the time 7 years have passed. The researchers concluded that these findings were consistent with their hypothesis that low-grade disease is at risk for progression to higher-grade lesions.

Other data, however, have suggested that low-grade disease does not progress to higher-grade cancer, but rather that high-grade lesions more likely develop from a clonally distinct population of cells. Penney et al.[34] hypothesized that if Gleason grade progression occurs during the natural history of prostate cancer, PSA screening should result in a reduction in the number of high-grade tumors diagnosed over time, similar to the well-documented stage migration that has occurred since the introduction of PSA screening. They confirmed that the proportion of patients in whom pT3 tumors were diagnosed dropped more than sixfold during the PSA screening era, from 19.5% (in 1982–1993) to 3% (in 2000–2004). The proportion of patients with a Gleason score of ≥ 8, however, decreased far more modestly, from 25.3% to 17.6%. When this was confined to men with T1/T2 disease, the reduction in the proportion of men with a Gleason score of ≥ 8 was only 19.5% to 16%. These researchers concluded that the lack of a decrease in high-grade tumors signifies that low-grade tumors do not progress to high-grade tumors, but rather that these high-grade tumors are arising de novo within the gland, and thus the lead time provided by PSA screening has failed to cull them from the population as would be predicted. It is important to note that these researchers regraded all specimens according to the 2005 ISUP modified Gleason system to avoid the potential bias caused by the upgrading of prostate cancer that has occurred over time.

Can Gleason 6 Progress to Higher-Grade Disease? Laboratory Evidence

Laboratory evidence attempting to answer the question of whether prostate cancers arise as well-differentiated lesions and then progress to more poorly differentiated tumors, or whether the histologic grade of the lesion is an early event in a lesion’s development, is also conflicting. A recent study by Sowalsky et al.[35] addressed this question by examining the status of the TMPRSS2:ERG gene fusion in prostate with adjacent foci of Gleason pattern 3 and pattern 4 disease. TMPRSS2:ERG gene fusions occur in approximately 50% of prostate cancers and are thought to be one of the early genetic events in the development of prostate cancer.[35] While it is known that tumor heterogeneity exists within a prostate, Sowalsky et al hypothesized that intermingled or adjacent glands of differing grades may come from a single clonal precursor and as such would most likely be concordant with respect to TMPRSS2:ERG fusion status. Consistent with their hypothesis, these investigators found 100% concordance between the TMPRSS2:ERG fusion status in 52 consecutive specimens with adjacent pattern 3 and 4 lesions. They confirmed this finding by analyzing the fusion breakpoints and again found that they were identical in the adjacent Gleason 3 and Gleason 4 glands. In a related study, researchers from the Mayo Clinic examined 14 patients with unifocal Gleason 7 prostate cancer and found that while there was significant genetic heterogeneity between adjacent Gleason pattern 3 and pattern 4 glands that composed a single Gleason 7 lesion, these two patterns also shared identical genetic alterations, indicating a common precursor.[37] These findings suggest that adjacent Gleason pattern 3 and 4 disease may come from a single common precursor lesion, supporting the concept of a stepwise progression of genetic insults in prostate cancer that...
may allow a Gleason pattern 3 lesion to progress to a more aggressive phenotype.
Kobayashi et al.[38] investigated 45 tumor foci from 22 radical prostatectomy specimens in patients
with pT2/3 disease and used comparative genomic hybridization to determine whether the multifocal
tumors present within the glands shared common genetic alterations, suggesting a common origin,
or had differing genetic profiles, suggesting several de novo tumors. They found that although there
was a single concordant genetic change between multifocal lesions in 13 of 22 (59%) of the
specimens, the vast majority of the genetic alterations were not concordant between lesions, and in
41% there was no concordance between the changes. They concluded that this suggests a
 multicentric origin rather than a single common genetic precursor cell that gives rise to all lesions
within a gland.

Gleason 6: Is It a Cancer?

This important question has significant clinical and public health implications. Unfortunately, there is
no simple answer. There are substantial limitations to our ability to accurately risk stratify detected
prostate cancers. As a result of random systematic biopsies, Gleason 6 disease often coexists with
undetected higher-grade disease. Some argue that this alone justifies labeling Gleason 6 disease as
a cancer.[39] We disagree. By extension of this guilt-by-association reasoning, high-grade prostatic
intraepithelial neoplasia and atypical small cell acinar proliferation, both of which are known to
coexist with undetected cancer, should be labeled as cancers. In fact, we know that many cancers
remain undiagnosed owing to a false-negative biopsy that shows only benign prostatic hyperplasia.
Is benign prostatic hyperplasia cancer? Where do we draw the line?

Our inability to confidently conclude that Gleason 6 disease is not a cancer is attributable to the
limitations in the sensitivity and specificity of our detection methods. The present challenge is to
improve the performance of screening and detection, thus avoiding the diagnosis of insignificant
cancers, which include the majority of screen-detected Gleason 6 tumors. We believe that the best
strategy for avoiding overtreatment of insignificant disease is not to diagnose it in the first place.
There is increasing evidence that the negative predictive value of a multiparametric magnetic
resonance imaging (mpMRI) scan for Gleason pattern 4 disease is exceedingly high.[40] If this is the
case, biopsies should be targeted to the focal abnormalities noted on mpMRI rather than performed
randomly throughout the gland as is done at present. This will allow for the detection of only disease
with a high likelihood of being clinically significant and will avoid detection of lesions likely to be
indolent and clinically irrelevant. There is also evidence that biopsy-detected Gleason 6 prostate
cancers with a propensity to progress may have unique genetic or biochemical signatures.[41] A
combination of targeted biopsy and assessment of genetic/biochemical signatures will likely result in
better risk stratification of Gleason 6 disease in the future. Equipped with this information, a rational
decision process can be applied for assignment to active surveillance, targeted therapy, or whole
gland management. As we progress toward a new paradigm for detection and risk stratification
of prostate cancer, there will likely be a decrease in the detection and treatment of true Gleason 6
tumors.

Conclusion

The preponderance of evidence suggests that true pathologic Gleason 6 disease, while possessing
the ability to grow and extend locally, has an exceedingly low, if any, metastatic potential. Therefore,
it is our opinion that today’s pathologic Gleason 6 disease should not be labeled as a cancer.
However, it remains to be determined whether Gleason 6 disease has the capacity over time to
transform and acquire a metastatic phenotype, and as such, we do believe this entity should be
differentiated from benign entities. Unfortunately, we can confidently diagnose true Gleason 6
disease only after the prostate has been removed. The future lies in developing a new paradigm for
screening and detecting prostate cancers that uses imaging and molecular tools to selectively
identify only cancers with a metastatic phenotype.

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