VOLUME 30 · NUMBER 35 · DECEMBER 10 2012

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

# Gleason Score 6 Adenocarcinoma: Should It Be Labeled As Cancer?

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Overtreatment of low-grade prostate cancer (Gleason score $\leq 6$) is a recognized problem today, with systematic prostate gland sampling triggered by prostate-specific antigen (PSA) measurements.[1] The extent to which overtreatment is caused by fear of death resulting from cancer, fear of litigation from undertreatment, and misaligned incentives that reimburse more for treating rather than monitoring when appropriate is not known. Nevertheless, fear of death resulting from cancer likely plays some role, and removing the label "cancer" could reduce unnecessary treatment of low-grade disease.[2,3] On the other hand, undertreatment of prostate cancer and a missed opportunity for cure in those who could benefit is a real risk of relabeling a cancer as noncancer. We have decided on an alternative modification of the Gleason scoring system and herein present the arguments for and against removing the label of cancer from Gleason 6 tumors. We believe that our alternative approach may help: one, ensure that patients receive the proper counseling/treatment; two, reduce the risk of overtreatment and its associated harms; and three, improve shared decision making.

## Rationale for Removing the Label of Cancer From Gleason 6 Tumors

*The updated Gleason grading system is misleading for patients and physicians.* The Gleason grading system, based on five architectural patterns of a tumor, has evolved over time.[4] For practical purposes, Gleason patterns (grade) 1 and 2, or scores 2 to 4 noted in the classic system, are not diagnosed on needle biopsies because of poor correlation with radical prostatectomy grade and poor reproducibility among expert pathologists.[5] The Gleason system has been modified based on a 2005 consensus conference,[4] whereby lesions previously referred to as Gleason scores 2 to 4 in the classic system are now assigned a higher grade (Gleason score 6) in the modified system; however, those previously graded as Gleason score 6 in the classic system are often graded as Gleason score 7 tumors in the modified system. Although this modification of grading could improve the prognosis of some men who have cancer-specific outcomes intermediate between the modified Gleason score 6 and the classical Gleason score 3 + 4 cancers,[6] the larger effect of the 2005 modification has been to improve the perceived cancer-specific survival by 26% through the Will Rogers phenomenon.[7]

Best evidence using robust end points from various sources, including competing risk analyses, surgical series, nonrandomized cohort studies, and randomized trials, has demonstrated the similarity of outcomes for men with Gleason score 6 tumors treated or not in the PSA era.[8-12] Taken together, these data demonstrate that using a time horizon of 10 to 15 years, less than 3% of men diagnosed with Gleason score $\leq 6$ and classified as low risk (based on a PSA $< 10$ ng/mL and stage $\leq$ T2a) will die as a result of prostate cancer whether treated or not. The evidence calls into question the need for treating men with Gleason score 6 tumors (graded in the modified system) who have a life expectancy of fewer than 10 to 15 years, especially if considered low risk.[13] But the reality is that today, men older than age 65 years with Gleason score 6 tumors on needle biopsy are treated as though they harbor a tumor with the same biologic potential as those with a Gleason score $\geq 7$[14,15]—a one-size-fits-all approach that is inconsistent with medical evidence suggesting that physicians and patients view a Gleason score 6 cancer today as a lethal phenotype in most cases.

*Fear induces overtreatment of prostate cancer.* In the National Cancer Institute Patterns of Care Study[16] and recent updates from the CAPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) registry,[14,17] approximately half of newly diagnosed men have Gleason score $\leq 6$ at diagnosis, and 80% to 90% depending on age undergo some form of treatment even when age at diagnosis is $> 75$ years. Raldow et al[18] recently reported that among men age 67 to 84 years with cancers labeled as low grade in the WHO classification scheme, one in three with an estimated life expectancy of $< 5$ years and 50% to 60% with an estimated life expectancy of 5 to 10 years underwent curative treatment with radiation or surgery. This clearly represents a large disconnect between evidence and practice. Although there may be multiple reasons for overtreatment of prostate cancer, fear of dying as a result of cancer surely plays a role in decisions to proceed with treatment among men with Gleason 6 tumors. Because patients generally interpret the assignment of Gleason score 6 as an intermediate cancer on a scale of 2 to 10, it is easy to see why most patients believe they harbor a lethal disease that needs immediate treatment.

## Rationale for Leaving the Label of Cancer Attached to Gleason Score 6 Tumors

*Morphologically and genetically, Gleason score 6 is cancer with the ability to invade tissues.* Gleason score 6 cancer is composed of Gleason pattern 3 cancer, which shares cytologic and molecular alterations

  

associated with higher Gleason patterns and has the ability to extend locally beyond the prostate and invade nerves. Gleason pattern 3 cancer harbors many of the molecular alterations associated with higher-grade cancers, including loss of the basal cell layer, overexpression of alpha-methylacyl-CoA racemase, glutathione *S*-transferase hypermethylation and downregulation, and *TMPRSS2-ERG* gene fusions.[19] The overlap in molecular alterations between Gleason pattern 3 and higher Gleason patterns suggests that the designation of cancer is appropriate.

*Biopsy Gleason score underestimates disease grade and extent.* On the basis of the intermediate end points of pathologic grade and stage, biopsy Gleason score underestimates both grade and extent of disease. Among men at a median age of 58 years who had at least a 10-core prostate biopsy, 36% of Gleason score 5 to 6 tumors were upgraded at radical prostatectomy if tertiary patterns were considered, and 25% were if tertiary patterns were not considered.[20] The rate of upgrading was 35% for Gleason scores 5 to 6 on biopsy to Gleason score $\geq 7$ at radical prostatectomy when studies that had evaluated at least 100 patient cases since 1992 were included.[20]

In addition to upgrading, men who are thought to harbor Gleason score $\leq 6$ on biopsy may have more extensive non–organ-confined disease. In a study evaluating men who met different criteria for enrollment in active surveillance, 70% to 80%, depending on inclusion criteria, were organ confined and Gleason score 6 on pathologic review of radical prostatectomy specimens.[21] Furthermore, among men chosen for active surveillance based on a Gleason score $\leq 6$ and treated surgically after a median of 1.3 years after enrollment, 80% had organ-confined disease.[22] Thus, one could argue that if one in three to one in five men thought to harbor Gleason score $\leq 6$ tumors actually have high-grade or non–organ-confined disease, assigning a noncancer moniker to these low-grade cancers would disadvantage a substantial proportion of men by delaying curative therapy.

The risk of upgrading from a biopsy Gleason score 6 to higher grade within the prostate correlates with multiple factors, including serum PSA levels, clinical stage, and extent of cancer on biopsy,[20] and the risk of harm from the cancer depends on age and the presence or absence of comorbidities. Although one could devise complicated rules for which Gleason score 6 tumors on biopsy should be called carcinomas and which ones should not, this would introduce an unreasonable level of complexity, not even factoring in that the definitions would change over time as new knowledge and techniques were acquired.

*Renaming Gleason score 6 tumors as noncancer could result in a missed opportunity for cure.* Because biopsy Gleason score underestimates both grade and disease extent, and because grade and disease extent are predictive of cancer-specific survival,[11,23] the identification of a Gleason score 6 cancer on biopsy is important information that could lead to earlier management, with an improved cancer-specific outcome, for two reasons. First, a biopsy Gleason score 6 tumor may reflect the presence of a higher grade or more extensive disease that was not sampled. If Gleason 6 on biopsy were not labeled as cancer, the potential for higher-grade or more extensive disease might be ignored, and physician recommendations (or compliance with recommendations) for immediate treatment or careful monitoring when appropriate might not occur. Second, a Gleason score 6 tumor on biopsy seems in a small percent of patients to progress to higher-grade carcinoma; although the rate of this progression is unknown, it presumably increases with time.[24] If labeled as a benign lesion, progression of Gleason score 6 cancer could be missed, resulting in treatment administered at an incurable stage.

*Renaming Gleason score 6 tumors as noncancer would result in medical liability.* Undoubtedly, renaming Gleason score 6 tumors as benign lesions would risk medical liability for pathologists and urologists.[25] Pathologists could be liable for underdiagnosing cancer, leading to a delay in diagnosis. Currently, medical liability is virtually unheard of for a pathologist who undergrades a carcinoma. Although the issue is one of semantics, the change in diagnosis from noncancer to cancer would seem to be more significant than one of grade change in a carcinoma, especially to a lay jury. Similarly, some urologists would be liable if they did not treat a tumor that was later discovered to be incurable.

## Modification of the Gleason Scoring System Retaining the Word Cancer and Emphasizing the Indolent Behavior of Gleason 6 Tumors

There is a precedent for retaining the term carcinoma for tumors that are indolent. For example, squamous cell carcinoma of the skin is a common tumor that like low-grade prostate carcinoma is morphologically carcinoma yet has a negligible risk of mortality. Patients are reassured about the typically benign clinical course of this tumor and consequently not overly concerned when diagnosed with carcinoma, accepting conservative treatment. Rather than avoid the term carcinoma, patients and physicians need to be educated about the indolent behavior of Gleason score 6 tumors and alternatives to immediate treatment.

In the absence of definitive markers of the lethal phenotype, a new paradigm is needed to express the risk associated with Gleason score 6 tumors. We propose to adopt at Johns Hopkins an alternative approach based on a modified Gleason scoring system referred to as prognostic grade group. Five prognostic categories will be reported based on prostate biopsy (Table 1). For men undergoing radical prostatectomy from 2004 to 2011, these prognostic grade groups from 1 to 5 have been associated with 5-year biochemical recurrence-free survivals of 94.6%, 82.7%, 65.1%, 63.1%, and 34.5%, respectively (Pierorazio et al, manuscript in preparation). These data are consistent with the literature supporting the concepts that on prostate biopsy: one, current Gleason score 6 tumors are more homogeneous and associated with better prognosis than in the past[7,26] because of reclassification of what was previously referred to as Gleason score 6 to Gleason score 7 today; two, as compared with Gleason score 3 + 4, Gleason score 4 + 3 is associated with a greater disease extent and higher rate of biochemical failure after curative intervention[27-29]; and three, when compared with Gleason score 8 tumors, Gleason scores of

**Table 1.** Gleason Score Prognostic Grade Groups

| Gleason Score | Prognostic Grade Group |
|---|---|
| $\leq 6$* | I/V* |
| 3 + 4 = 7 | II/V |
| 4 + 3 = 7 | III/V |
| 8 | IV/V |
| 9-10 | V/V |

*A man's risk of death as a result of prostate cancer is similar whether treated or not over 10 to 15 years after diagnosis if associated with low clinical stage (T1c to T2a) and prostate-specific antigen < 10 ng/mL.[1]

9 and 10 are associated with lower rates of freedom from disease after curative intervention.[30] However, we acknowledge that 5-year biochemical recurrence-free survival is only an intermediate end point, and longer follow-up is necessary to determine if these prognostic groupings will be associated with more robust clinically meaningful end points.

We believe that this system retains the proven prognostic value of the Gleason system[4] and allows continued comparison with older literature, while emphasizing for patients and physicians that Gleason score 6 should be considered in the context of a prognostic category of 1 of 5, not 6 of 10. In addition, the reporting emphasizes that based on the conclusions of a recent National Institutes of Health Consensus Conference,[1] those men with low-risk disease (Gleason score 6, PSA < 10 ng/mL, and clinical stage T1c to T2a) who are untreated have a similar cancer-specific survival when compared with those treated over 10 to 15 years after diagnosis. It is hoped that this will alleviate some of the fear associated with a diagnosis of Gleason score 6 "cancer" and give patients a more realistic perspective regarding their prognosis whether treated or not.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Provision of study materials or patients:** Alan W. Partin
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

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DOI: 10.1200/JCO.2012.44.0586; published online ahead of print at www.jco.org on October 1, 2012

  