Low-Grade Prostate Cancer: Time to Stop Calling It Cancer

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Introduction

Prostate-specific antigen (PSA) screening for prostate cancer (PCa) remains highly controversial, largely because it is unclear whether the primary benefits of reducing rates of metastases and cancer mortality are worth the risks of overdiagnosis, overtreatment, and potential treatment-related morbidity. A major contributing factor to overdiagnosis and overtreatment is the designation of a particular pattern of low-grade cellular changes in the prostate as cancer, which, in our view, should not be called cancer. A simple terminology change for these lesions and removal of the cancer label would dramatically reduce overdiagnosis and overtreatment and markedly change the cost-benefit calculus of PSA screening. Although proposed previously,[1,2] it never became a widespread discussion with material impact. We feel that revisiting this proposal is timely, compelling, relevant, and of utmost importance.

The histologic grading system for PCa encompasses remarkable diversity—from nearly universal indolence (Gleason score [GS] 6) to almost certain eventual lethality (GS10)—and drives nearly all management decisions in localized PCa. We review the inert clinical behavior of GS6 PCa, ongoing concerns regarding widespread overdiagnosis and overtreatment, and the rationale for a change in nomenclature.

GS6 Histology is Highly Prevalent

After rapid and pervasive adoption of PSA-based early detection efforts in the United States, the age-adjusted PCa-specific mortality decreased by 50% and is certainly reason for celebration.[3] However, the unintended consequences of this pyrrhic victory adversely affected millions of men diagnosed with and treated for cancers never destined to alter their quality or quantity of life.[4] PCa incidence doubled,[5] with low-grade cancers such as GS6 (ie, Grade Group 1) accounting for up to 70% of new diagnoses.[2,3] The root of the overdiagnosis epidemic stems from > 30% of men over age 50 (more than 60% by age 80) years harbor histologic PCa, as microscopic PCa ultimately develops in nearly all prostates if a man lives long enough.[4,5] Yet, only 3% of all men eventually die of PCa.[3] GS6 is largely a natural, age-related histologic observation defined artefactually as a disease, not known to cause symptoms or metastases,[6] but paradoxically leads to invasive monitoring or treatment. These concerns were a primary factor contributing to the US Preventive Services Task Force categorically discouraging PCa screening in 2012, specifically noting the common diagnosis and treatment of "microscopic, well-differentiated lesions…unlikely to be clinically important."[7]

Low-Grade Prostate Cancer Behaves Clinically Like Precancer Rather Than Cancer

A common definition of cancer is a "malignant tumor (which) can invade and destroy adjacent structures and spread to distant sites,"[8] a view generally shared by the nonmedical public.[9] Although GS6 meets the pathologic criteria of a cancer (invasion of the stroma), without the simultaneous presence of higher-grade disease (GS ≥ 7; ie, Grade Group ≥ 2), it is effectively incapable of invading adjacent local structures[10] or metastasizing.[11] When a prostate is surgically removed and contains only GS6, there is essentially a 100% chance of remaining metastasis-free[12] although the cancer has typically been present for years and often decades. When a cancer-related death rate approaches 0%, even in the absence of treatment, consideration should be given to modifying the screening, diagnostic, management, and terminology paradigms.

Contemporary Detection and Management of GS6 Reflects a Precancer Rather Than Cancer

Modifications to early detection paradigms have occurred and are ongoing. Indiscriminate screening is less common, but remains highly prevalent. Novel blood and urine biomarkers and magnetic resonance imaging (MRI) have been integrated into diagnostic pathways as secondary tests to identify higher-grade cancers while attempting to minimize the number of men diagnosed with GS6.[13-15] Clinical management of GS6 has dramatically changed following institutional series, clinical trials, and population-based data showing superb long-term outcomes with various forms of conservative management (ie, active

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surveillance),[16-19] including similar PCa mortality rates compared with matched populations of men *without* PCa.[20] Consequently, active surveillance is now a global standard of care[21] and used frequently, in up to 80% of men with low-risk PCa in Sweden,[22] Canada,[23] and parts of the United States.[24] However, in many countries and most regions of the United States, underutilization of active surveillance remains common[25] as many physicians—both primary care doctors and PCa specialists—continue to routinely recommend treatment.[26]

GS6 Should be Renamed

Concordant with these commendable efforts in modifying screening, diagnosis, and management, strong consideration should also be given to eliminating the word cancer from GS6. PCa experts have previously debated reclassification of GS6 and removal of the cancer label.[1,2,27] Similarly, a Centers for Disease Control and Prevention (CDC) State-of-the-Science Consensus meeting in 2012 on the role of active surveillance in the management of men with low-risk PCa recommended the development of new terminology to replace the word cancer and supported the classification of low-risk lesions as indolent lesions of epithelial origin.[28] However, the massive issue of overdiagnosis and overtreatment persists. Revisiting this discussion should be a high priority within the PCa community.

Reclassifying cancer has precedent—in prostate (GS 2 through 5),[29] bladder,[30] cervical,[31] and thyroid cancers[32]—and has been discussed for other cancers such as breast (low-grade ductal carcinoma in situ)[33] and melanoma (Fig 1).[34] A commonality among many of these cancers is the high prevalence of indolent disease in the healthy population. Although not a new conversation in PCa, the compelling supportive data amplify the urgency of the message.

Advantages of Renaming GS6

Reclassification of GS6 would immediately lead to markedly fewer diagnoses of PCa; fewer men receiving radiation, surgery, and other treatments; fewer men experiencing treatment-related side effects; lower patient and family anxiety; and substantial reductions in financial burden to individuals and the health care system.[35] No matter how much time a physician may spend downplaying the significance of a GS6 diagnosis or emphasizing the phrase low-risk, the words "you have cancer" have a potent psychological effect on most men and their families.

A PCa diagnosis has been associated with an increased risk of depression and suicide,[36] even when low-grade, despite negligible risk of cancer-related harm. Even when a patient chooses surveillance, family or friends of patients may often find the decision to live with untreated cancer bizarre. Frustratingly, when purchasing life insurance policies, the diagnosis can lead to disqualification or considerably higher rates. Since many guidelines and policymakers advocate shared decision making,[37] it is critical to consider

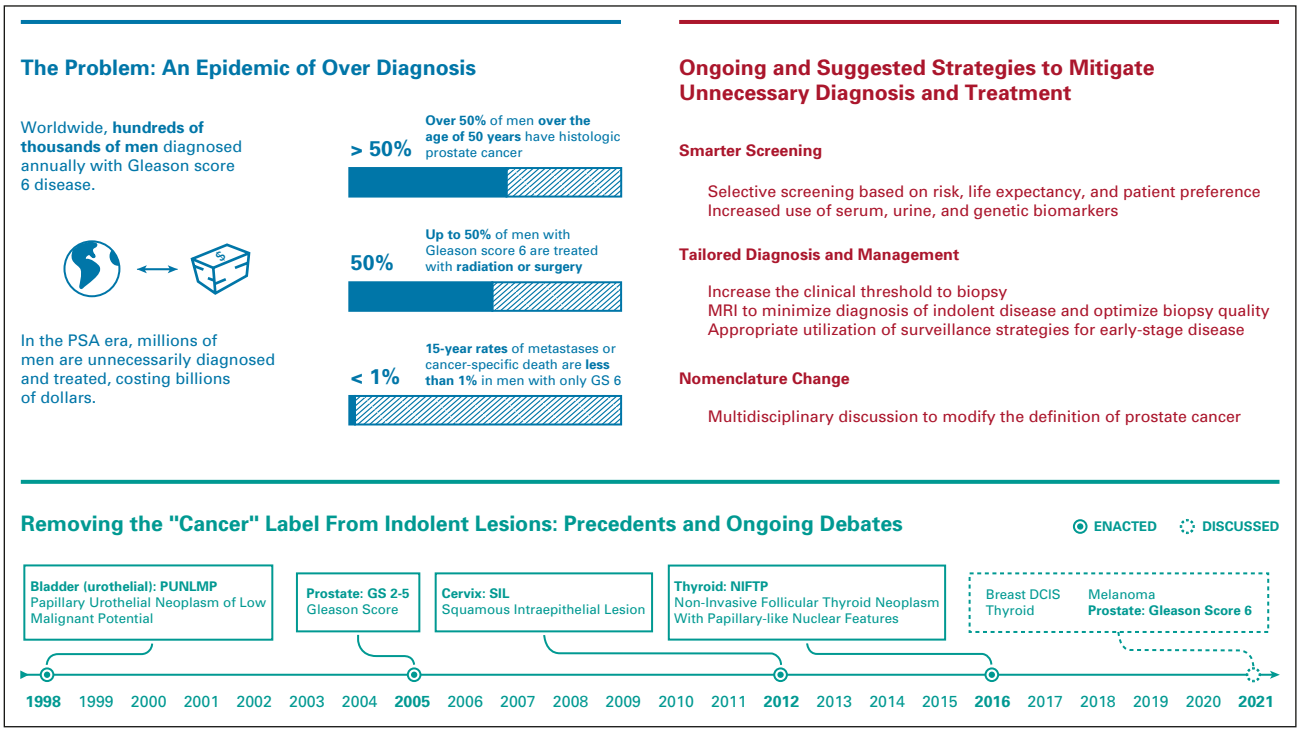

FIG 1. Low-grade prostate cancer: prevalance of overdiagnosis, mitigation strategies, and historical parallels. DCIS, ductal carcinoma in situ; PSA, prostate-specific antigen.

a more patient-centric disease labeling to promote clarity and understanding, provide value, and limit undue harm.

Common Counterarguments to Renaming GS6

The most common counterargument for preserving the current nomenclature is that up to 30% of men with GS6 on biopsy who undergo surgery are found to harbor higher-grade cancers.[38] Nonetheless, the presence of higher-grade cancers unsampled on biopsy does not demonstrably alter long-term oncologic outcomes.[39] The flawed rationale of routinely treating men with GS6 on biopsy on the basis of the possibility of unsampled higher-grade cancers would be similar to treating a man with a negative biopsy on the basis of similar concerns, a strategy that would universally be considered improper. In the contemporary era—with MRI, image-directed biopsies, more extensive biopsy sampling templates, restaging biopsies during surveillance, and integration of genomic biomarkers—rates of identifying higher-grade cancers on subsequent biopsy in men whose initial biopsy showed GS6 are strikingly similar (20%-30%) to rates of identifying higher-grade cancers among men who undergo surgery for GS6 on biopsy.[40]

Advocates of preserving the status quo of categorizing GS6 as cancer suggest that active surveillance with PSA, digital rectal examination, and intermittent biopsies (with or without MRI) are essential to diagnose previously unidentified or newly formed higher-grade cancers in a timely fashion. Relabeling GS6 would not lead to recategorizing these biopsies as normal, and therefore, a diagnosis would still indicate a similar approach of serial PSA (with or without other biomarkers), digital rectal examination, and MRI (with or without biopsies). By analogy, colon polyps warrant a varying intensity of surveillance and endoscopy on the basis of the risk profile, but without the label of cancer, they preclude any question of routine colectomy or chemoradiation therapy.

Another criticism of the proposed nomenclature change is that approximately 15% of GS6 cancers have molecular similarities to higher-grade cancers.[41] Although true, this is challenging to reconcile with, to our knowledge, the absence of any patient with pure GS6 ever experiencing a metastasis or death from the cancer. GS6 labeled something other than cancer would still require surveillance, and since the window of opportunity for curing localized PCa is typically measured in years or decades, evidence of histologic progression to a higher-grade cancer would far precede the potential time of future metastasis in the majority of cases.

There may be legitimate concerns about patient compliance with ongoing surveillance for a precancerous lesion, potential delays in diagnosing higher-grade cancers, debate over the intensity and type of follow-up, and impact on longer-term cancer outcomes. Similar concerns were raised when GS 2-5 tumors were reclassified (to noncancers or GS6) and when active surveillance for low-grade PCa was introduced in the mid-1990s. Countless other clearly positive transformations in PCa and throughout the oncology and medical sciences were initially and continuously met with doubt and even scorn, yet proven unequivocally correct by history.

Intent of Contemporary Prostate Cancer Screening

Most experts agree that the modern objective of PCa screening in an otherwise healthy man who chooses to undergo screening is to identify GS $\geq$ 7 cancers while curtailing the diagnosis of GS6. Accordingly, the National Comprehensive Cancer Network (NCCN) PCa Early Detection Guidelines state that screening should "improve the identification of significant cancer while avoiding the detection of indolent disease".[42] What is a better way to avoid the detection of GS6 than to retire its cancer label entirely?

Radical treatment for a relabeled GS6 may one day be considered inappropriate and unjustifiable in most cases. We envision a landscape in which treatment for localized PCa would nearly always require the presence of GS $\geq$ 7 or other objective evidence of adverse biology. Similar to current management of noncancerous prostate lesions such as high-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation, a variety of individualized risk-stratified screening options would be available for erstwhile GS6, including ongoing screening, biomarkers, imaging, and rebiopsy.

Renaming GS6 is Important for Public Health

A sensible path forward requires input from many stakeholders, including pathologists, urologists, radiation oncologists, patients, and partners. The exact relabeling is not pertinent except for it not including cancer, as most people understandably associate the word with an aggressive and possibly lethal malady. Regardless of what tempering terms might be used, if the disease label includes cancer, it affects mental health, modulates decisions and behavior, and increases tolerance for treatment-derived toxicities.[43] In breast cancer, as in PCa, nomenclature directly affects the likelihood of patients electing aggressive treatment.[33,44] Every PCa clinician observes this phenomenon on a regular basis.

The conversation is necessary and should be multidisciplinary, but the ultimate nomenclature decision will depend on genitourinary pathologists, ideally with input from other specialists and patient advocates. We feel that platforms within individual specialty meetings, multidisciplinary conferences, and even symposiums singularly focused on GS6 are key to addressing this important public health issue.

Even if GS6 is biologically inert, its labeling is not, as it has an important influence and tangible consequences on how patients, providers, and the general public react and

respond. We believe that a name change should be thoroughly discussed, vetted, and ultimately adopted. If ultimately deemed appropriate, there will be predictable and unforeseen obstacles, requisite educational campaigns, and large-scale implementation efforts. Nevertheless, we feel that rescinding the cancer label from GS6 would dramatically improve individual and public health. The data are compelling, the moral imperative is sound, and the time is overdue.

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REFERENCES

1. Ahmed HU, Arya M, Freeman A, et al: Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? Lancet Oncol 13:e509-517, 2012
2. Carter HB, Partin AW, Walsh PC, et al: Gleason score 6 adenocarcinoma: Should it be labeled as cancer? J Clin Oncol 30:4294-4296, 2012
3. Islami F, Ward EM, Sung H, et al: Annual report to the nation on the status of cancer, Part 1: National Cancer Statistics. J Natl Cancer Inst 113:1648-1669, 2021
4. Welch HG, Albertsen PC: Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. J Natl Cancer Inst 101:1325-1329, 2009
5. Cancer of the Prostate—Cancer Stat Facts. SEER. https://seer.cancer.gov/statfacts/html/prost.html
6. Labbate CV, Paner GP, Eggener SE: Should Grade Group 1 (GG1) be called cancer? World J Urol 40:15-19, 2022
7. Moyer VA; US Preventive Services Task Force: Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 157:120-134, 2012
8. Robbins Basic Pathology—10th Edition. https://www.elsevier.com/books/robbins-basic-pathology/kumar/978-0-323-35317-5
9. "cancer." 2021. https://www.merriam-webster.com
10. Anderson BB, Oberlin DT, Razmaria AA, et al: Extraprostatic extension is extremely rare for contemporary Gleason Score 6 prostate cancer. Eur Urol 72:455-460, 2017
11. Ross HM, Kryvenko ON, Cowan JE, et al: Do adenocarcinomas of the prostate with Gleason score (GS) ≤6 have the potential to metastasize to lymph nodes? Am J Surg Pathol 36:1346-1352, 2012
12. Eggener SE, Scardino PT, Walsh PC, et al: Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol 185:869-875, 2011
13. Eklund M, Jäderling F, Discacciati A, et al: MRI-targeted or standard biopsy in prostate cancer screening. N Engl J Med 385:908-920, 2021
14. Kasivisvanathan V, Rannikko AS, Borghi M, et al: MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 378:1767-1777, 2018
15. Narayan VM: A critical appraisal of biomarkers in prostate cancer. World J Urol 38:547-554, 2020
16. Klotz L, Vesprini D, Sethukavalan P, et al: Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 33:272-277, 2015
17. Tosoian JJ, Mamawala M, Epstein JI, et al: Active surveillance of Grade Group 1 prostate cancer: Long-term outcomes from a large prospective cohort. Eur Urol 77:675-682, 2020
18. Wilt TJ, Jones KM, Barry MJ, et al: Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 377:132-142, 2017
19. Hamdy FC, Donovan JL, Lane JA, et al: 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 375:1415-1424, 2016
20. Rider JR, Sandin F, Andrén O, et al: Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. Eur Urol 63:88-96, 2013
21. Chen RC, Rumble RB, Loblaw DA, et al: Active surveillance for the management of localized prostate cancer (Cancer Care Ontario guideline): American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 34:2182-2190, 2016
22. Loeb S, Folkvaljon Y, Curnyn C, et al: Uptake of active surveillance for very-low-risk prostate cancer in Sweden. JAMA Oncol 3:1393-1398, 2017
23. Timilshina N, Ouellet V, Alibhai SM, et al: Analysis of active surveillance uptake for low-risk localized prostate cancer in Canada: A Canadian multi-institutional study. World J Urol 35:595-603, 2017
24. Loeb S, Byrne NK, Wang B, et al: Exploring variation in the use of conservative management for low-risk prostate cancer in the Veterans Affairs Healthcare System. Eur Urol 77:683-686, 2020
25. Tyson MD, Graves AJ, O'Neil B, et al: Urologist-level correlation in the use of observation for low- and high-risk prostate cancer. JAMA Surg 152:27-34, 2017

26. Archana R, Wallner LP, Skolarus TA, et al: Primary care physician perspectives on low risk prostate cancer management: Results of a national survey. Urol Pract 8:515-522, 2021
27. Eggener SE, Badani K, Barocas DA, et al: Gleason 6 prostate cancer: Translating biology into population health. J Urol 194:626-634, 2015
28. Esserman LJ, Thompson IM, Reid B, et al: Addressing overdiagnosis and overtreatment in cancer: A prescription for change. Lancet Oncol 15:e234-42, 2014
29. Epstein JI, Allsbrook WC Jr, Amin MB, et al: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 29:1228-1242, 2005
30. Miyamoto H, Miller JS, Fajardo DA, et al: Non-invasive papillary urothelial neoplasms: The 2004 WHO/ISUP classification system. Pathol Int 60:1-8, 2010
31. Darragh TM, Colgan TJ, Cox JT, et al: The lower anogenital squamous terminology standardization project for HPV-associated lesions: Background and consensus recommendations from the college of American Pathologists and the American Society for Colposcopy and Cervical Pathology. J Low Genit Tract Dis 16:205-242, 2012
32. Nikiforov YE, Seethala RR, Tallini G, et al: Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: A paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2:1023-1029, 2016
33. Omer ZB, Hwang ES, Esserman LJ, et al: Impact of ductal carcinoma in situ terminology on patient treatment preferences. JAMA Intern Med 173:1830-1831, 2013
34. Welch HG, Mazer BL, Adamson AS: The rapid rise in cutaneous melanoma diagnoses. N Engl J Med 384:72-79, 2021
35. Trogdon JG, Falchook AD, Basak R, et al: Total Medicare costs associated with diagnosis and treatment of prostate cancer in elderly men. JAMA Oncol 5:60-66, 2019
36. Carlsson S, Sandin F, Fall K, et al: Risk of suicide in men with low-risk prostate cancer. Eur J Cancer 49:1588-1599, 2013
37. US Preventive Services Task Force, Grossman DC, CurrySJ, et al: Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA 319:1901-1913, 2018
38. Thaxton CS, Loeb S, Roehl KA, et al: Treatment outcomes of radical prostatectomy in potential candidates for three published active surveillance protocols. Urology 75:414-418, 2010
39. Kovac E, Vertosick EA, Sjoberg DD, et al: Effects of pathological upstaging or upgrading on metastasis and cancer-specific mortality in men with clinical low-risk prostate cancer. BJU Int 122:1003-1009, 2018
40. Ahdoot M, Wilbur AR, Reese SE, et al: MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 382:917-928, 2020
41. Cooperberg MR, Erho N, Chan JM, et al: The diverse genomic landscape of clinically low-risk prostate cancer. Eur Urol 74:444-452, 2018
42. Carroll PR, Parsons JK, Andriole G, et al: NCCN guidelines insights: Prostate cancer early detection, version 2.2016. J Natl Compr Canc Netw 14:509-519, 2016
43. Robb KA, Simon AE, Miles A, et al: Public perceptions of cancer: A qualitative study of the balance of positive and negative beliefs. BMJ Open 4:e005434, 2014
44. Hudnall MT, Desai AS, Tsai KP, et al: It's all in the name: Does nomenclature for indolent prostate cancer impact management and anxiety? Cancer 127: 3354-3360, 2021

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