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Platinum Opinion

Removing the Designation of Cancer from Grade Group 1 Disease Will Do More Good than Harm

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Netto et al [1] argue against recent proposals to avoid the term "cancer" when only grade group 1 (GG1) disease is found on prostate biopsy. One "strong rationale" is that "pattern 3 cancer shares many morphologic and canonical molecular alterations associated with higher-grade prostate adenocarcinoma" [1]. This provides a clear contrast to the views of advocates for redesignating pattern 3 as noncancer. As published researchers, we are certainly interested in debates about histopathologic or molecular categorization. For instance, we agree entirely that a subset of GG1 tumors harbor molecular alterations that may presage eventual progression to clinically meaningful disease [2], but would point out that the same is true of histologically normal prostate tissue [3]. A critical argument is that GG1 disease generally lacks several molecular hallmarks associated with malignancy, in particular the capacity to metastasize [4]. We would ask why lack of basal cells rather than capacity for metastasis should be used to distinguish cancer from noncancer.

However, the foundation for our argument in favor of redesignation is not an academic debate about categorization, it is 100% a matter of patient-centered, practical outcomes. What matters is what will happen in clinical practice and public health if we continue to call GG1 disease "cancer" and what will happen if, instead, we redesignate it as an abnormality with a label other than "cancer".

The practical arguments for dropping the term cancer for GG 1 disease are as follows.

(1) **The word "cancer" has a very specific and highly adverse emotional resonance.** Many patients say that the day on which they were told "You have cancer" was the worst day of their life. Anxiety related to a diagnosis of prostate cancer has been well documented [5] extending as far as an increase in the risk of suicide [6]. No matter how well intentioned and committed to active surveillance a diagnosing clinician may be, this cultural connotation will not abate in the foreseeable future.

(2) **Overtreatment of low-grade prostate cancer remains rife.** Despite more than a decade of intense advocacy for active surveillance, more than 40% of men in the USA with low-risk disease are treated immediately—with far higher rates in some practice settings—meaning that many tens of thousands of men continue to undergo unnecessary surgery and radiotherapy annually [7].

(3) **The word "cancer" causes overtreatment.** It is harder to get men to opt for active surveillance for prostate cancer exactly because we have called it cancer [8].

(4) **Treatment criteria remain porous, raising the risk of overtreatment.** The past few years have seen numerous back-and-forth changes to eligibility for active surveillance, including those for stage, prostate-specific antigen (PSA) characteristics, positive cores, and percentage core involvement. Most recently, some urologists have started to use genomic

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tests, recommending treatment to patients with low-grade disease if genomic risk is high. Predictably, this has led to a decrease in the use of active surveillance, particularly among the least educated [9], despite large cohort studies showing superb long-term outcomes for surveillance in cohorts of men with low-grade cancer, many of whom would presumably have had high genomic risk [10].

(5) **A diagnosis of cancer has unavoidable social implications.** Having a history of cancer—regardless of indolent modifiers—has a multitude of negative effects on relationships [11], employment [12], and insurance [13].

(6) **Avoidance of the term cancer does not obviate treatment or monitoring.** If there is good evidence of benefit, we routinely treat premalignant conditions across numerous organ sites. This extends to radical surgery such as mastectomy, oophorectomy, and even gastrectomy for patients with high-risk germline mutations. Similarly, we routinely monitor patients without a cancer diagnosis, such as those with polyps on colonoscopy, precancerous skin lesions, or predisposing conditions such as Lynch syndrome. Indeed, in prostate cancer, we carefully follow men with high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) and even those with high PSA after negative biopsy. Relabeling GG1 as something other than "cancer" absolutely does not imply that it would be called "normal", any more than we would call, say, a colon polyp "normal". GG1 disease would still require monitoring on a formal active surveillance protocol, and could be subject to treatment given a compelling reason.

Let us now evaluate the arguments raised by Netto et al [1], which are in common with those of other proponents for retaining the current prostate cancer nomenclature.

(i) **Patients will not adhere to surveillance unless they are told they have cancer.** "If one were to drop the cancer label ... adherence to intensive monitoring and the option to choose definitive therapy could be jeopardized" [1]. There are no data to suggest that we must scare patients into appropriate monitoring by use of the word "cancer"; quite conversely, we monitor many precancerous conditions, such as colon polyps and abnormal nevi, without labeling them with a cancer diagnosis. For prostate cancer, we have no problem following men with elevated PSA and negative biopsy or other lesions such as HGPIN or ASAP; these are monitored closely, often with the same tools as active surveillance for prostate cancer.

(ii) **Redesignation of pattern 3 will lead to litigation**: Redsignation "may raise legal risks related to potential grading disagreements" [1]. There is no evidence that the legal problems will be worse for "cancer/no cancer" compared to "cancer serious enough to treat/-cancer that does not need treatment".

(iii) **Overtreatment is an easily solvable problem**: What is most critical is "education for surgeons and patients [about] the vital role of AS". Overtreatment continues to be a major problem despite many years of advocacy and education.

(iv) **Dropping the cancer label for GG1 will lead to undertreatment:** "needle biopsy may significantly underestimate the final grade ... even in academic high-volume centers, targeted biopsies miss clinically significant cancers ... [this will be worse in] low-volume community practice setting[s]" [1]. Whether pattern 4 is the criterion for treatment or the criterion for a cancer diagnosis makes no difference to the problem of biopsy sampling error. Moreover, the problem of undersampling is more apparent than real: the long-term risk of cancer mortality for patients with negative sextant biopsy is extremely low [14], as is the risk of mortality for patients who are undergraded at biopsy [15].

(v) **Failing to call pattern 3 cancer will lead to undue repeat biopsy**: "One can anticipate a significant increase in the proportion of cases for which repeat biopsy is needed because of equivocal diagnoses ... reported by concerned pathologists" [1]. This concern applies today no less in cases of ASAP, for example, and clinicians are well able to evaluate which men need closer monitoring and repeat assessments with imaging, biomarkers, and biopsy. There are no empirical data to support an increase in unnecessary repeat biopsy associated with redesignation.

In summary, points 1–6 in favor of redesignation are based on data published in the literature or follow well-established oncologic practice. Conversely, points i–v in favor of maintaining the cancer designation are speculative at best, and disproven at worst.

There is, no doubt, comfort in the status quo, and it certainly does seem extreme to rename one of the commonest forms of one of the commonest cancers as a noncancer. But extreme problems call for extreme measures, particularly when more tempered approaches have failed to solve a major problem dramatically affecting US public health. We are now in our fourth decade of prostate cancer overdiagnosis and overtreatment. We have caused extraordinary harm not only directly, through anxiety and treatment side effects, but also indirectly, by discouraging screening [16], thereby resulting in avoidable cancer mortality. There is undoubtedly a histopathologic rationale for keeping pattern 3 as cancer. But try explaining that to a patient harmed by overtreatment or dying of prostate cancer because his doctor made a currently defensible recommendation against PSA screening. If practical outcomes are the goal, the evidence is clear: redesignate pattern 3 and avoid the word "cancer" for patients with GG1 disease.

Conflicts of interest: Andrew Vickers is co-inventor of 4kscore, a commercially available reflex test for predicting prostate biopsy, and may receive royalties from sales of the test. He owns stock options in Opko, which offers the test, and also has financial relationships with Arctic Partners, Steba, and Insightec. Matthew R. Cooperberg and Scott E. Eggener have nothing to disclose.

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