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Title

Reply to A. Azad et al

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Journal

Journal of Clinical Oncology, 31(26)

ISSN

0732-183X

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Publication Date

2013-09-10

DOI

10.1200/jco.2013.51.4919

Peer reviewed

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DOI: 10.1200/JCO.2013.51.0420; published online ahead of print at www.jco.org on August 12, 2013

Reply to A. Azad et al

We appreciate Azad et al's comments,¹ which center on questions regarding the clinical application of the cell cycle progression (CCP) score. We would stress that the purpose of our article² was to validate the score's accuracy in a contemporary prostatectomy cohort. To this end, we demonstrated that the score does in fact yield additional, independent information about progression risk, independent of all standard clinical and pathologic information. Our study was not designed to determine the optimal use of the score in clinical practice; answering this question will require additional research, ongoing at our institution and elsewhere.

To address the specific points Azad et al raise¹: first, we agree that most tumors with pathologic Gleason score 6 typically do not progress to metastasis or mortality after surgery, and we certainly do not advocate indiscriminate use of any adjunct testing for all men with these tumors. However, it should be stressed that we explored interactions between CCP score and clinical/pathologic risk, as determined by the Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) score, and found that the CCP score was predictive across the range of CAPRA-S scores.

Furthermore, Gleason score should not be interpreted in a vacuum; some Gleason 6 scores are associated with other higher risk characteristics (high preoperative prostate-specific antigen, higher stage, positive margins, and so on). Conversely, some Gleason 7 tumors with minimal representation of pattern 4 and no other adverse risk characteristics behave no differently from Gleason 6 tumors.³ Ultimately, risk assessment must consider all available information and identifying which tumors with one or more high-risk features might benefit from additional treatment would be potentially beneficial.

We agree entirely that active surveillance is under-used for low-risk disease in the United States and have repeatedly made this argument in prior publications.^{4,5} Azad et al's first point was that the CCP score may be more useful for tumors with adverse risk factors such as Gleason 7. So, if anything, the score should be more useful in the setting of clinical cohorts with higher average progression risk.

With respect to the question of postoperative radiation selection and timing, we did not claim that the CCP score would settle the question of adjuvant versus early-salvage radiation. We agree studies in cohorts re-

ceiving radiation are needed, and these studies are ongoing. In the interim, the score should be interpreted only as providing additional information about progression risk, which can help inform a clinical decision; we have not proposed an algorithm to determine which men should get radiation based the CCP score, either alone or together with the CAPRA-S.

Finally, we agree that the number of options for additional testing among men with prostate cancer is obviously growing rapidly. However, most of these tests—including the ones referenced in Azad et al's¹ letter—have not been validated to date nearly as rigorously as the CCP score. Determining the relative merits of the CCP score in relation to these other tests was well beyond the intended scope of our validation study but, again, is the focus of ongoing research. Specifically with respect to multiparametric magnetic resonance imaging, we agree this modality is likely to have a future role in helping improve active surveillance protocols.⁶ This modality still depends on very experienced radiologists with a high degree of prostate expertise, and—at least in the United States—is extremely expensive relative to other emerging tests.

Our validation study² on the CCP score is clearly not presented as the end of the story for improved risk stratification, nor is it even the beginning of the end.⁷ We are only starting to learn how best to use cancer genomic assays⁷ and other emerging tests to help improve decision-making for men with prostate cancer. However, there is no question that innovative tests like this one will be essential to help effect the needed paradigm shift in prostate cancer screening, diagnosis, and management—to one in which decisions at all time points reflect full use of the maximal information available.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's

conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Matthew R. Cooperberg, Myriad Genetics (C), Genomic Health (C), GenomeDx (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Peter R. Carroll, Myriad Genetics, Genomic Health **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

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DOI: 10.1200/JCO.2013.51.4919; published online ahead of print at www.jco.org on August 12, 2013

Sirolimus Reduces Cutaneous Squamous Cell Carcinomas in Transplantation Recipients

TO THE EDITOR: Hoogendijk-van den Akker et al¹ investigated the aggressive nature of some cutaneous squamous cell carcinomas (SCCs) in selected solid organ transplantation recipients. In these patients, SCC contributes to significant morbidity as a result of extensive field disease and numerous primary cancers as well as mortality secondary to metastases. We were also interested in two similar randomized control trials by Euvrard et al² and Campbell et al.³

All three groups report a decrease in the number of SCC in at least one study arm on revision of immune suppression through conversion to sirolimus. Prior reports have shown that reduction or discontinuation of immune suppression leads to a decrease in the incidence and severity of SCC. More recent studies have suggested that switching to sirolimus, an mammalian target of rapamycin (mTOR) inhibitor with antiproliferative effects, may reduce the frequency and severity of SCCs.

A major finding from the Hoogendijk-van den Akker et al¹ and Euvrard et al² studies was that the greatest reduction in the development of future SCCs at 1 year and 2 years after conversion to sirolimus, respectively, was observed in patients who had developed a single SCC before conversion to sirolimus. Both studies found a nonsignificant reduction of subsequent SCCs in patients who had numerous SCCs before conversion to sirolimus, or those with catastrophic cutaneous carcinomatosis.⁴ These studies suggest that conversion to sirolimus should be considered earlier than previously proposed by guidelines of the International Transplant Skin Cancer Collaborative, possibly on the development of a single SCC (Table 1). Another option for the revision of immunosuppression includes decreasing the dose of immunosuppressant agents. Alternatively or in conjunction, chemoprophylaxis with the vitamin A analog acitretin can reduce the number of new SCCs in transplantation recipients.⁵ These results also point to the importance of identifying alternative strategies for treating patients whose disease have already progressed to catastrophic disease.

It should be noted that conversion to sirolimus may be complicated as a significant number of patients developed adverse events after switching to sirolimus. Euvrard et al² report serious adverse events in 94% of patients receiving sirolimus, often resulting in at least temporary discontinuation of the drug. Thus, transplantation neph-

Table 1. Consider Revision of Immunosuppression With the Following Clinical Outcomes

- 5 to 10 well-differentiated SCCs per year
- One SCC with \geq two AJCC-defined high-risk features*
- Recurrent SCC
- SCC with in-transit metastases
- Metastatic SCC

Abbreviations: AJCC, American Joint Committee on Cancer; SCC, squamous cell carcinoma.

*Breslow tumor thickness greater than 2 mm, Clark level \geq IV (into the reticular dermis), perineural invasion, anatomic site (ear, nonglabrous lip), and degree of histologic differentiation (poorly differentiated or undifferentiated).

rologists are often justifiably reluctant to change immune suppression to sirolimus in patients with functional allografts.

We stress that revision of immune suppression will not result in cure but can be part of a comprehensive multidisciplinary approach to decreasing the disease burden of skin cancer. Despite the use of safer immunosuppressant agents, transplantation recipients will continue to require vigilant dermatologic follow-up through frequent comprehensive total body skin examinations.

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ACKNOWLEDGMENT

Written on behalf of the Immunology Working Group of the International Transplant Skin Cancer Collaborative.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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