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European Association of Urology

Letter to the Editor

Re: Melissa Assel, Anders Dahlin, David Ulmert, et al. Association Between Lead Time and Prostate Cancer Grade: Evidence of Grade Progression from Long-term Follow-up of Large Population-based Cohorts Not Subject to Prostate-specific Antigen Screening. Eur Urol 2018;73:961–7

Assel et al. [1] recently presented data on the time from elevated prostate-specific antigen (PSA) to prostate cancer diagnosis. They found that men diagnosed with high-grade disease had a longer time from elevated PSA to diagnosis, and conclude that Gleason grade progresses. We believe that the data they presented do not support such an inference.

The article did not describe the time period or the source of Gleason grade information. Gleason grading has changed dramatically over time, with more patients assigned a higher grade in recent years [2]. Without contemporaneous re-review of the original biopsy tissue, changes in grading practice alone would lead to the appearance of more high-grade cases being diagnosed later in time, further from the baseline PSA measurement.

As the authors point out, age is associated with higher Gleason grade, but this does not mean that grade progresses within an individual. Since the participants were (of course) older at later times in the study, it is possible that some had undiagnosed low-grade tumors early in the study and then developed separate high-grade tumors diagnosed at an older age; however, the lower-grade tumors could still be present.

This study calls attention to the challenges of attempting to answer the question of Gleason progression within individuals. As the authors note, repeat biopsy studies showing upgrading in active surveillance patients could be due to initial undersampling. This apparent upgrading could also be affected by differences in patients who return for a follow-up biopsy, as well as the increasing risk of new high-grade tumors with increasing age.

We previously explored this topic using a population-based approach [3]. Widespread adoption of PSA screening led to a remarkable reduction in the incidence of advanced prostate cancer at diagnosis (stage shift). Since stage progression occurs, we reasoned that Gleason progression, if present, would also be revealed by a parallel decrease in the incidence of high-grade disease. We found that despite the extreme changes in clinical stage over decades, the incidence of high-grade disease (on the basis of pathologist re-review) remained fairly constant over decades within our cohorts. This suggests that Gleason grade progression is not common, although we cannot rule out its occurrence in rare individuals.

Additional pathology evidence suggests that grade does not progress. Prostate cancer is multifocal, and grade can appear to increase with the development of a new, higher-grade tumor focus. Adjacent tumor foci of different grades can have different molecular profiles suggesting that they arose independently, and that the higher grade did not progress from the lower grade. Metastases typically have the same grade as the primary tumor; an autopsy study found no difference in cellular differentiation between the primary tumor and metastases [4].

The question of Gleason progression is of major importance for the treatment of prostate cancer; if Gleason grade does progress, then radical treatment of low-grade disease has a stronger rationale. However, current data do not strongly support Gleason grade progression.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Assel M, Dahlin A, Ulmert D, et al. Association between lead time and prostate cancer grade: evidence of grade progression from long-term follow-up of large population-based cohorts not subject to prostate-specific antigen screening. Eur Urol 2018;73:961–7.
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