Do Gleason patterns 3 and 4 prostate cancer represent separate disease states?

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Abstract

PURPOSE: The Gleason scoring system has been the traditional basis for studies on the assessment and treatment of prostate cancer. Recent reports of long-term prostate cancer outcomes stratified by Gleason score based on the 2005 ISUP (International Society of Urological Pathology) update suggest that important aspects of the biology of prostate cancer correlate with commonly available histopathological information. In this review we present a conceptual framework for the possible existence of distinct but interrelated developmental pathways in the context of the Gleason score in considering various biological and clinical aspects of prostate cancer. This may be useful in characterizing prostate cancer as an indolent condition in some and an aggressive disease in others, in decision making for treatment, and in the interpretation of the biological course and treatment outcomes.

MATERIALS AND METHODS: A comprehensive review of clinical, pathological and investigational biological literature on this topic was conducted. In addition, the biological behavior of prostate cancer as interpreted from this survey was compared to that of other solid neoplasms in developing a schema for characterizing the pathogenesis of various forms of the disease.

RESULTS: The Gleason scoring system has been found to have fundamental value in predicting the behavior of prostate cancer and assessing outcomes of its treatment. Increasingly, the proportion of Gleason pattern 4 in a prostatectomy specimen is being recognized as a critical factor in predicting the rates of biochemical recurrence and prostate cancer specific mortality. Under the current Gleason classification, a Gleason 3 + 3 = 6 cancer carries a minimal long-term risk of progression or mortality. Risk of biochemical recurrence and prostate cancer specific mortality increases with increasing proportions of the Gleason 4 component in the prostatectomy specimen, from 3 + 3 = 6 with tertiary 4 (ie less than 5% of a 4 component) to 3 + 4 = 7, 4 + 3 = 7 and 4 + 4 = 8. Assuming that the Gleason 4 component increases in volume more rapidly with time than well differentiated components, it can be inferred that a smaller proportion of Gleason 4 could mean that the cancer has been identified at an earlier phase in the natural history of the disease. This could explain the improved prognosis on the basis of length and lead time biases, and conceivably on the basis of a decreased likelihood of cancer cells having metastasized. Correspondingly, increasing amounts of Gleason 4 cancer in a prostate specimen might be explained in 2 ways, as the preferential growth of a single clone of Gleason 4 cells, possibly with intraprostatic spread, or the evolution of Gleason 3 cancer cells to become Gleason 4. These hypotheses have been examined by genetic analysis of metastatic deposits and by comparisons of multiple foci of cancer within individual prostates. The clinical significance of these concepts in regard to disease status at diagnosis, treatment selection, outcomes of treatment, and implications for future research on the basis of clinical and molecular observations are the basis of the developmental schemata we propose.
CONCLUSIONS: Given the relatively benign nature of homogeneous, low volume Gleason 3 tumors, and the progressive risk of biochemical recurrence and prostate cancer specific mortality with increasing quantities of Gleason 4 components, we propose that Gleason 4 (and 5) cancers constitute cancer diatheses distinct from that of Gleason 3 cancer. This distinction may contribute to the understanding of the prognosis intrinsic to these biological behavioral patterns, and help guide the translation of findings at molecular and histological levels to a more precise selection of treatments.

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