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LETTER TO THE EDITOR

Disease-Free Survival and Time Bias in Long-Term Follow-Up After Complete Resection of Localized Well-Differentiated Cancer

TO THE EDITORS:

Recently, Vorburger et al. presented a "long-term follow-up after complete resection of well-differentiated cancer confined to the thyroid gland."[1] To create a "highly selected group of 186 patients with macroscopically localized disease and microscopically confirmed complete resection of the carcinoma," patients with evidence of tumor extension beyond the thyroid capsule, positive margins, enlarged lymph nodes, or distant metastasis were excluded. Institutional follow-up was complete for 166 patients who underwent various operations between 1972 and 1990.

Clinical outcome studies frequently use the endpoint "disease-specific survival" (DSS) as an adjunct to overall survival (OS). Both endpoints can be calculated by actuarian methods, censoring patients with incomplete observations at last follow-up pending further information. OS, representing the converse of all-cause mortality, is a straightforward measure comparatively easy to ascertain. DSS rates, among other factors, hinge on the correct adjudication of cause of death (cancer versus intercurrent disease), rendering the DSS more vulnerable to bias.[2] The authors explicitly acknowledged this limitation: "Due to the long follow-up period, disease-free survival could not be reliably determined."

In the absence of information on what the authors considered as cancer-specific mortality, this cautionary statement leaves the reader at a loss for what these patients died of specifically. Once local control is achieved in the neck, distant metastases, which reportedly were excluded, are the leading cause of cancer-specific death. Occult lymph node metastases may progress to gross metastases but, if cleared promptly, rarely cause cervical obstruction. The same applies to locoregional recurrence from a thyroid remnant or the thyroid bed (multifocal/multiple tumors or unappreciated extrathyroidal extension), which originate only exceptionally from incidental cancers.

Misclassification should be relevant particularly to patients from the 1970s, a time when imaging technologies were in their infancy (computerized tomography) or virtually nonexistent (high-resolution ultrasonography). Likewise, better surgical techniques have increasingly permitted the clearance of recurrent tumor from the neck that used to be considered as inoperable in former times.

As a matter of fact, any evidence of differential diagnosis, staging, or treatment over time ("time bias") would violate Kaplan-Meier assumptions.[3] These premises demand that every single patient in the analysis be given the same chance of receiving the same tumor stage and the same treatment, irrespective of time. A greater level of detail regarding the causes of "cancer-specific" mortality is imperative to enable the reader to determine the impact of "time bias" and the applicability of the authors' DSS estimates to current medical practice.

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