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EDITORIAL – HEPATOBILIARY TUMORS

Use of Large Retrospective Databases to Guide Tumor Staging Criteria

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The presence of hypoxia within solid tumors is a well-documented phenomenon that plays a complex role in tumorigenesis both through direct effects promoting coagulative necrosis, and more indirect effects on gene expression mediated through hypoxia-inducible factor-1α (HIF-1 α).[1] Hypoxia and resultant necrosis often are observed in aggressive tumors, giving rise to the theory that rapid proliferation causes tumors to outgrow their own blood supply. Intratumoral hypoxia is reflected on histopathologic analysis by the presence of tumor necrosis, which has been associated with aggressive phenotypes and poor long-term outcomes in a variety of tumor types including breast, pancreatic, renal cell, and bladder cancer.[2–5]

In this issue of *Annals of Surgical Oncology*, Tsilimigras et al. examine the prognostic implications of the presence of tumor necrosis on histopathologic examination from 757 patients with intrahepatic cholangiocarcinoma using data maintained by the International Intrahepatic Cholangiocarcinoma Study Group, which collects data from 15 major hepatobiliary centers around the world.[6] Not only did they find the presence of necrosis to be associated with other risk factors for higher risk disease, such as tumor size, higher preoperative CA19-9, and poor/undifferentiated grade, but also that it was associated with both a lower median 5-year recurrence-free survival (RFS) and overall survival (OS) in patients with tumors staged as T1 by current 8th edition American Joint Committee on Cancer (AJCC) criteria. The authors propose new staging criteria for T1 tumors, in which the presence of necrosis would upstage a T1a to a T1b, and subsequently a T1b to a T2 tumor. Using multivariable survival regression, their staging system demonstrated an improved model fit in predicting patient survival outcomes compared with the existing staging system.

The development of international multicenter databases has been instrumental to the development and validation of staging systems, especially in relatively rare tumors, such as intrahepatic cholangiocarcinoma. However, there are limitations to databases that are not prospectively maintained, including incongruent and missing data. Indeed, of the patients examined by the authors, 32% of the initial cohort (n = 1,143) were missing either follow-up data (n = 193) or pathologic data (n = 174)—a significant proportion of the studied population. Ideally, staging systems developed from examination of one database would be validated by application in another database, although existence of parallel databases containing similar variables can make this often impossible. This is one potential explanation for why to date, tumor necrosis has not yet been incorporated into any AJCC TNM staging criteria for other pathologies. An example demonstrating a potential pitfall of large databases was seen after the development of the AJCC 8th edition for gallbladder carcinoma in which T2 tumors were subdivided into T2a and T2b based on tumor location: peritoneal side versus hepatic side. This was in part based on data from an international multicenter study of 437 patients, which showed a worse prognosis in patients with hepatic sided T2 tumors compared with peritoneal sided T2 tumors.[7] Interestingly, when examined in a cohort of 1,251 patients with T2 gallbladder carcinoma using the National Cancer Database (NCDB), a retrospective database of patients in the United States, tumor location was not associated with differential survival on multivariable cox

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regression analysis.[8] This illustrates the importance of cross-validation of staging systems, ideally with more than one dataset, in particular when data are collected retrospectively, when feasible.

Two additional points of consideration before incorporation of a histopathologic factor into a staging system are 1) the possible effect of treatment on that factor, and 2) the collection and availability of the factor for application. In the case of tumor necrosis, treatment strategies, such as portal vein embolization, radiation, and neoadjuvant chemo- and immunotherapy, have the potential for altering the inherent content of necrosis in a tumor, thereby influencing the proposed stage. As to the availability of the factor for analysis, any staging criteria must be universally collected to allow for wide applicability. Because tumor necrosis is currently not mentioned in the most recent AJCC staging manual, it is likely not routinely collected as a measure uniformly at institutions worldwide, another potential explanation why it is not yet part of any AJCC staging.[9]

Regardless of their inherent limitations, international multicenter databases remain a powerful tool for our understanding of rare cancers. Implementation should be done with consideration of potential confounding factors and critical validation.

DECLARATIONS

DISCLOSURE The authors declare no conflicts of interest.

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