Artificial Intelligence in Cancer Staging: Limitless Potential or Passing Fad?

John W. Kunstman, MD, MHS^{1,2}

¹Department of Surgery, Section of Surgical Oncology, Yale University School of Medicine, New Haven, CT

²VA Connecticut Health System, West Haven, CT

In this issue of *Annals of Surgical Oncology*, a distinguished group of international coauthors utilized a novel machine learning approach to modeling prognosis in patients with intrahepatic cholangiocarcinoma (ICC).¹ Using a database spanning four continents, Tsilimigras and colleagues of the International Intrahepatic Cholangiocarcinoma Study Group found that tumor number, tumor size, albumin-bilirubin grade (ALBI), and preoperative lymph node involvement were most predictive of overall survival among patients undergoing resection for ICC. Of these findings, perhaps only ALBI will be unfamiliar to some practitioners; it is a metric for assessing liver function that was originally defined in patients with hepatocellular carcinoma but was recently shown to be prognostic in ICC as well by the current Study Group.^{2,3} Based on these four criteria, operative patients could be stratified four subgroups with excellent discrimination of overall survival.

It will come as no surprise to hepatobiliary surgeons that patients with ICC featuring large or multifocal tumors, regional lymphatic spread, or poor liver function will suffer comparatively poor survival next to their counterparts with more favorable disease characteristics. The staging of ICC, which was evaluated jointly with hepatocellular carcinoma until the 6th edition of the American Joint Committee on Cancer (AJCC) staging system, remains challenging and many have noted the shortcomings of the AJCC's current 8th edition.^{4,5} In that context, this study makes a strong argument for altering the surgeon's approach to

management and more strongly weighing liver function in selecting patients for resection. For instance, patients with three or more tumors were found to have survival inferior to those with metastatic disease (AJCC stage 4) despite undergoing resection. Surgeons continue to debate whether multifocal ICC signifies metastatic or locoregional (satellitosis) disease, and these data strongly argue that resection offers minimal benefit to patients with multiple tumors except in very highly selected cases. As more data accumulates, the iterative refinement of ICC staging and selection for surgery will surely continue to improve.

Certainly, a deeper analysis of the prognostic features of ICC is both noteworthy and valuable to surgeons. However, the most significant contribution of the manuscript by Tsilimigras et al. is its methodology. As bigger and more inclusive datasets are amassed in many areas of medicine (nicely illustrated by the international database analyzed here), investigators must search for new ways to transform these resources into usable information.^{6,7} Broadly speaking, machine learning techniques, such as the Classification And Regression Tree (CART) predictive modeling employed here, offer an attractive way to analyze large datasets to determine patterns and trends. CART modeling was first described in 1984 by Breiman and is one of the most useful applications of machine learning.⁸ In CART analysis, patterns are determined computationally via inference, mimicking the human process of learning by example.^{9,10} Thus far, applications have been wide-ranging but with a particular focus on clinical prediction and prognostic models.^{11,12} Logistic regression, the traditional modeling technique for these applications, remains a key approach but relies on known rules and variables fixed by the investigator.¹³ Machine learning, when unsupervised, allows significant output variables to be deduced in an unbiased fashion, possibly revealing previously unknown

patterns or findings. Savvy human investigators remain crucial to the process in order to determine which of these findings are not only statistically significant but have real clinical relevance.

Tsilimigras et al. illustrate both the great promise and potential drawbacks of using machine learning in analyzing surgical datasets. As the availability of ever-larger datasets continues to improve, the quality of the input data continues to be the limiting factor in attempts to answer practice-changing questions. For ICC, these questions include not only candidacy for surgery as examined here but also selection for neoadjuvant or adjuvant systemic therapy, best surgical approach, the role of transplantation, and many others. Addressing these questions requires large datasets of greatly increased granularity. Other applications of artificial intelligence, such as natural language processing of electronic medical records, hold promise in addressing these shortcomings. Conventional statistical approaches, such as logistic regression, will continue to be important, but machine learning will prove to be a major addition to the investigator's toolkit, especially in datasets vulnerable to bias. In the future, the opening efforts of Tsilimigras and colleagues will prove to be prescient as efforts to refine surgical decision-making are augmented by this powerful new approach.

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