Rather than categorizing all multifocal disease as "liver metastasis," patients with multiple ICC can harbor "true" multifocal tumors, a solitary tumor with satellite lesions, as well as intrahepatic liver metastasis. Failing to differentiate "multifocal tumors" into separate categories may have conflated three different clinical scenarios. Resection of multifocal ICC has been associated with worse outcomes versus patients who underwent surgery for a solitary tumor (5-year survival 30% versus 19%).[2] Survival was particularly poor in the setting of > 3 tumor nodules, nodal metastasis, and poor differentiation. However, patients with multifocal disease who had none of these factors had 5-year survival of 28% after resection—similar to patients with a solitary tumor. As such, patients with multifocal disease likely represent a heterogeneous population. Unfortunately, in the study by Lamarca et al. treatment details were not elucidated, which would have been important to understand relative to long-term survival.

The authors also did not thoroughly examine the impact of multiple ICC tumors relative to nodal status. Our group has long advocated for routine performance of lymphadenectomy.[3,4] Pathological assessment of the nodal basin is critical to staging as nodal status is among the strongest ICC prognostic factors.[5] Patients with concurrent multifocal tumors and lymph node metastases had a 5-year survival of 3.2%, which was worse than patients with either risk factor alone (12.8%) or patients with unifocal disease and no lymph node metastasis (28.8%).[2] Categorizing all patients with multifocal disease—regardless of nodal status—as M1a may not be accurate.

In sum, the authors' attempt to refine the current American Joint Committee on Cancer staging system relative to patients with multifocal disease is provocative. However, rather than simply categorizing all patients with multiple lesions as having M1a disease, a more nuanced approached informed by anatomic location of the lesions, other competing risk factors, as well as emerging molecular profiling will be needed.

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REPLY:

We thank Zhang and colleagues for their Letter to the Editor[1] regarding our work.[2] Our manuscript ("Liver Metastases of Intrahepatic Cholangiocarcinoma: Implications for an Updated Staging System"[2]) suggested changes to the American Joint Committee on Cancer (AJCC) staging classification for intrahepatic cholangiocarcinoma (iCCA) by classifying "liver metastases" as stage IV rather than stage II/III in the absence/presence of lymph node metastases, respectively, as per AJCC v.8.[3]

Firstly, regarding the methodology, we would like to highlight that the median follow-up (11 months) was a reflection of the short prognosis of this disease (all-stage data were included). Data maturity was adequate for overall survival (OS) analysis with 75.3% ("whole European Network for the Study of Cholangiocarcinoma") and 82.3% (Surveillance, Epidemiology, and End Results

Registry) of patient deaths at the time of analysis. Model discrimination (for both AJCC v.7 and our proposed modified version [mAJCC v.8]) was assessed and reported in our manuscript; we employed Harrell's C-index rather than the AUC since OS was explored as a continuous variable (not dichotomized), maximizing the power and granularity of information included.[4] We identified that "Harrell's C-index was slightly higher for mAJCC v.8 (C-index 0.624) than for the AJCC v.7 (C-index 0.614)." Although small, these changes still support the adequate OS prediction of our proposed staging system; the fact that only 17.3% of patients were reclassified using mAJCC v.8 is likely to explain this small change. Calibration analyses (not included in our manuscript) showed good calibration at 12 months (mAJCC v.8 mean error 0.007 [90th percentile 0.008] versus AJCC v.7 mean error 0.04 [90th percentile 0.091]).

Secondly, regarding potential clinical confounding factors, we accept that categorizing all multifocal disease as "liver metastases" without granularity on whether multifocal disease was due to true metastases, satellite lesions, or multiple primaries is a limitation of the study. Without tumor clonality assessment, it is not possible to identify "true" multiple primaries. In addition, multiple primaries in iCCA are rare and unlikely to impact the main findings from our study; this is supported by studies identifying the existence of a common progenitor cell of origin for multifocal iCCA[5] together with the fact that only a minority of iCCA arise in the background of cirrhosis (9.2%) or primary sclerosis cholangitis (1.7%).[2] In addition, almost half of patients had prior surgery (detailed in Table 1[2]); thus, even in the event of multifocal disease actually being satellite lesions (more likely to be resected), the main study conclusions would remain. Finally, a sensitivity analysis for nodal status confirmed that liver metastases were prognostic independently of nodal status, suggesting that both N0 and N1 scenarios should be classified as stage IV disease in the presence of multifocal liver disease.

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Letter to the Editor: Intravital Dynamic and Correlative Imaging Reveals Diffusion-Dominated Canalicular and Flow-Augmented Ductular Bile Flux

TO THE EDITOR:

The report by Vartak et al.[1] uses a technique for evaluating hepatic bile formation. They conclude that canalicular water flow does not occur, thus challenging the Sperber hypothesis. The validity of their technique for studying canalicular water flow awaits confirmation in other laboratories. Also, the investigators need to address the many reported studies that support the Sperber hypothesis.

Often, hypotheses are made that cannot be tested directly because of the lack of suitable experimental designs. Perhaps the most famous is the general relativity hypothesis. Initial support was obtained only when an eclipse occurred and the degree to which light waves were bent in passing the moon could be determined.[2]

The Sperber hypothesis, that water flows into the canalicular conduit in response to an osmotic gradient,[3] cannot be tested directly because canalicular flow cannot be measured. Micropuncture, a technique for collecting fluid from different regions of the nephron, has not thus far been technically successful because of the smaller diameter of the canalicular conduit.

Nevertheless, it is currently accepted that both the canalicular conduit and the cholangiocyte-lined bile ducts contribute the water that comprises hepatic bile.

Support for the Sperber hypothesis of canalicular water flow was obtained in a study by Meyers et al.[4] (Fig. 1). A low dose of estradiol-17 glucuronide