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EDITORIAL – HEPATOBILIARY TUMORS

Predicting Recurrence Patterns Following Curative-Intent Resection for Intrahepatic Cholangiocarcinoma

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Intrahepatic cholangiocarcinoma (ICC), based on margin status alone following a curative-intent resection, has a 5-year overall survival ranging between 4.7% (R1) to 39.8% (R0).[1] Alaimo and colleagues investigated the application of the hazard function for assessing hazard rates and patterns of recurrence following curative-intent ICC resection using a multi-institutional database.[2] They identified 1192 patients who underwent curative-intent resection for ICC between 1990 and 2020, and used the recurrence-free survival (RFS) hazard function to plot hazard rates over time. Smoothed estimates of hazard function were stratified by nodal status, tumor size, tumor burden score, and adjuvant chemotherapy. They concluded hazard function-based recurrence data may be helpful for counseling patients, determining surveillance strategies, and guiding adjuvant therapy.

The study is a part of a growing body of literature investigating possible avenues for improved and personalized surveillance schemes for patients with cancer.[3–5] Current surveillance strategies, as the authors note, do not have data to support a specific schedule. The most recent National Comprehensive Cancer Network guidelines, for instance, are based on the surveillance strategy employed in the phase III BILCAP trial.[6] They recommend, regardless of R0 or R1 resection status, that patients receive a computed tomography/magnetic resonance imaging (CT/MRI) of the abdomen/pelvis along with a CT of the chest every 3–6 months for 2 years, and then every 6–12 months for up to 5 years. How then, if at all, should we consider adjusting current surveillance strategies when the majority of patients with ICC (75%) develop recurrence in the first 2 years following curative-intent resection; a third of whom develop recurrence in the first 6 months?[7,8]

The authors' use of a large multi-institutional database to interrogate surveillance patterns for this rare cancer following curative-intent resection through the lens of hazard function spotlights a potentially useful tool. They observed significant heterogeneity in recurrence peaks among subgroups. In their cohort of patients, a majority (86.7%) of whom received R0 resections, the hazard function of recurrence peaked at 6.6 months. Intrahepatic recurrence typically occurred first (8.4 months) compared with extrahepatic (10.8 months). Tumor size, nodal stage, tumor burden score, and adjuvant chemotherapy all had varying effects on recurrence hazard.

Patients with T2 tumors were observed to have the earliest recurrence hazard peak at 4.8 months, while T4 tumors had the latest recurrence hazard peak at 12.6 months. This finding was likely the result of patients with T2 tumors being less likely to undergo lymphadenectomy at time of surgery. The authors reported patients with T2 disease had the highest rate of undetermined lymph nodes, a relatively low probability of receiving adjuvant chemotherapy, and a relatively high rate of multifocal disease.

A broader variance pattern for peak recurrence hazards was observed across T stages with N1 disease. Recurrence hazard peaks for T1N1, T2N1, T3N1, and T4N1 disease were 7.5 months, 8.2 months, 25.2 months, and 14.4 months, respectively. Such variance was lost when not stratified by T stage. Peak recurrence hazards for NX, N0, and N1 disease were 7.2, 6.6, and 6.6 months, respectively.

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Seeking to examine the significance of their previous work with tumor burden score,[9,10] the authors stratified tumor burden score into three groups (low, medium, and high) and observed a less pronounced variance in peak recurrence hazards. Patients with high tumor burden score were identified to have an early recurrence hazard peak at 4.2 months, whereas patients with low tumor burden score had a recurrence hazard peak at 6 months, and medium tumor burden score had a recurrence hazard peak at 7.2 months.

Their examination of the impact of adjuvant chemotherapy on recurrence hazard peaks revealed slightly more variance. Patients who did not receive adjuvant chemotherapy had an earlier recurrence hazard peak (6 months) compared with those who received adjuvant chemotherapy (13.2 months). The recurrence hazard peaks were slightly shortened in patients with N1 disease. Patients with N1 disease who did not receive adjuvant chemotherapy had a recurrence hazard peak at 5.4 months. Patients with N1 disease who received adjuvant chemotherapy had a recurrence hazard peak at 9.2 months.

Limitations include the retrospective nature of this study, the long study period, and there being differences in treatment strategies across the study period, but those aside, the authors have demonstrated a potential tool for optimizing surveillance strategies for patients with ICC after curative-intent resection. Its clinical impact, however, remains to be seen, as the use of the hazard function in this capacity has been applied for other malignancies without effect to surveillance guidelines.[11–16] The instantaneous nature of hazard functions makes event estimation difficult.[17] Hazard function conveys the instantaneous conditional rate of event risk (in this case recurrence) for patients who remain event free at the queried event time. One should note that the observed hazard is the average hazard of a heterogenous group of individuals with different underlying risk profiles. Therefore, the hazard function will always decrease over time and represent an apparent time-dependent pattern, as the high-risk patients fail early, while low-risk patients tend to remain in the study. Accordingly, it can be challenging to precisely determine whether the hazard truly changes its pattern, especially in late follow-up owing to estimation uncertainty.

In this analysis, the primary endpoint was recurrence-free survival. The so-called cause-specific hazard for recurrence was used in hazard estimation, which treats the competing events (e.g., secondary primary cancers, deaths prior to recurrence) as censoring and isolates their impacts when estimating the hazard for recurrence. The estimated hazard function was smoothed through kernel density smoothing, a moving weighted average of the data within a prespecified window or "neighborhood." Different choices of bandwidth (window width) substantially impact the smoothness and the pattern of the hazard function.[17] The authors should consider reporting the kernel bandwidth for the purpose of generalizability and reproducibility in future surgical oncology research.

Moreover, given the data-dependent nuances surrounding hazard function, the authors should consider providing guidance as to how the tool might best be used for individualized surveillance and adjuvant therapy. Mirroring the recurrence patterns for this disease, most recurrence hazard peaks occurred within the first 2 years after surgery. Current surveillance guidelines allow for cross-sectional imaging at 3-month intervals for 2 years. Should providers consider clustering more frequent surveillance imaging around reported recurrence hazard peaks? Would 2-month surveillance intervals clinically impact prognostication and adjuvant therapy?

It is worth remembering that, while surgical resection remains curative for a select cohort of patients with ICC, only 10–40% of patients present with resectable disease at time of diagnosis.[18,19] In this regard, developing personalized surveillance schemes will require a predictive tool that utilizes factors beyond nodal status, tumor size, tumor burden score, and adjuvant chemotherapy; an understanding of genomic landscapes paired with improved systemic therapies will be paramount.[20,21] It would be interesting to know whether the authors examined genetic data, biomarkers, patterns of recurrence, and/or neoadjuvant therapy with hazard function. We commend the authors for pushing personalized surveillance and demonstrating a novel approach for characterizing recurrence patterns.

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