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OPINION ARTICLE

Predicting outcomes of surgical management of intrahepatic cholangiocarcinoma: A Gordian Knot

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Summary

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy with liver resection with curative intent being the mainstay of treatment related to prolonged survival. Better risk stratification models are needed to optimize patient selection and identify individuals who will benefit the most from an operative approach or alternative treatments due to high incidence of recurrence in patients undergoing resection with curative intent for ICC. Machine learning as well as markers of tumoral biology can generate reliable models that could help in identifying patients at risk of recurrence and worse outcomes. Liver transplantation might have a role in patients with small unresectable tumors.

Key words: *intrahepatic cholangiocarcinoma, resection, transplantation, recurrence, machine learning*

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy after hepatocellular carcinoma (HCC), however the incidence of ICC has been increasing worldwide over the last two decades [1]. Liver resection with curative intent is the mainstay of treatment related to prolonged overall survival (OS) for patients with ICC. The optimal approach depends on the anatomical site of the primary tumor and the best outcomes are achieved through management by specialist multidisciplinary teams. Unfortunately, most patients present with locally advanced or metastatic disease [2,3]. Thus, the prognosis of these patients is still dismal since recent studies report a 5-year OS of 30% after surgery [4,5].

Factors such as pathological features including vascular invasion (VI), tumor differentiation, tumor size, tumor number, lymph node metastasis, and surgical resection margin have been identified to play an important role in predicting outcomes of patients with ICC [4,6]. Among them, tumor size is a primary determinant of prognosis for many cancers and integrated into various staging systems to guide treatment and predict prognosis [7]. In the 8th American Joint Committee on Cancer (AJCC) cancer TNM staging system for ICC, tumor size is used to differentiate T1 into T1a (≤ 5 cm) and T1b (>5 cm), while T2 is classified based on VI and tumor number, and T3 and T4 are defined based on the invasion of surrounding tissues or organs [8]. The effect of tumor size on survival in ICC has been reported in many studies [9]; however, the results in these explorations were inconsistent in terms of both the prognos-

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tic ability and the identification of optimal cut-off values. The ambiguous status of tumor size as a factor in prognosis and the imprecise cut-off point for the diameter could influence the reliability of the existing staging systems and predicting models and is definitely affecting the selection of treatment strategy and the prediction of prognosis [10]. Another challenge in the management of patients with ICC is the fact that approximately 60% of patients with resectable tumors will recur within 2 years of surgery, while 25% of patients will recur in the first 6 months after curative-intent resection [11]. Thus, better risk stratification models are needed to optimize patient selection and identify individuals who will benefit the most from an operative approach or alternative treatments. The thesis of the present opinion piece is that management of ICC remains a Gordian Knot for surgeons and thus better prognostic schemas should be developed to identify patients who are at risk of early recurrence and might be eligible for alternative management algorithms incorporating neoadjuvant chemotherapy and transplantation.

Role of tumor size in classification schemas and surgical management

The relationship between tumor size and survival in ICC is still a matter of debate. It is shown that patients with large tumors have worse OS than small tumor size groups, and tumor size is an independent prognostic factor for OS for solitary ICC after resection, both for patients with and without VI. However, the optimal cut-off values for solitary ICC with and without VI were recently found to be 8 and 3 cm respectively, that could divide the patients into two groups with significant differences in OS. Thus, the existing AJCC staging system might need to be improved if the cut-off value of the T1 stage was changed to 8 cm and if the T2 stage incorporated a tumor size with a cut-off value of 3 cm [12].

Tumor size should also guide the magnitude of surgical resection. Currently, major hepatectomy is more frequently offered to ICC patients who had large, multiple, and bilobar tumors, however it is more related to higher incidence of postoperative morbidity. Of interest, a recent propensity matched analysis showed patients who underwent major hepatectomy had an equivalent OS and recurrence-free survival (RFS) vs patients who had a minor hepatectomy (median OS, 38 vs. 37 months, p=0.556; and median RFS, 20 vs. 18 months, p=0.635). Moreover, patients undergoing major resection had comparable OS and RFS with wide surgical margin (≥10 and 5-9 mm), but improved RFS when surgical margin was narrow (1-4 mm) vs minor resection [13]. These findings are similar to recent data reported from HCC literature [14]. Also, a recent NSQIP analysis showed that in patients with primary liver malignancies (HCC and ICC), elective major resection in patients with a MELD score equal or greater than 10 is related to a 10% 30-day mortality [15], which is not-acceptable in the elective setting. These findings further support the role of non-anatomic liver resections in patients with ICC in the frame of oncological equipoise.

Nodal disease and ICC

The prevalence of nodal metastases detected at the time of surgery for ICC has been reported as 25-50% [16]. The literature suggests that nodal metastasis is significantly associated with poor survival outcomes in patients who undergo hepatic resection for IHC [4,17]. However, the oncologic value of lymph node dissection in resected IHC is still controversial [18]. A recent online calculator has been proposed to predict nodal metastases by incorporating clinical and imaging data (https://k-sahara.shinyapps.io/ICC_imaging/). The c-index of the model was 0.702 and outperformed the preoperative imaging alone (c-index 0.660). The predicted 5-year OS for low-risk patients was 48.4% compared to 18.4% of high-risk patients, p<0.001). When applied among Nx patients, 5-year OS and RFS of low-risk Nx patients was comparable with that of N0 patients, while high-risk Nx patients had similar outcomes to N1 patients (p=NS) [19]. In the same setting, patients with ICC and 1 or 2 positive nodes (LNM) had comparably worse OS to patients with no nodal disease (median OS, 1 LNM 18.0, 2 LNM 20.0 vs no LNM 45.0 months, both p< 0.001), yet better OS vs patients with 3 or more LNM (median OS, 1-2 LNM 19.8 vs ≥3 LNM 16.0 months, p<0.01). These findings generated the proposal of a new nodal staging with N1 (1-2 LNM) and N2 (≥3 LNM) since these categories were independently associated with incrementally worse OS and RFS (both p<0.05). Also, a total number of greater or equal to 6 examined nodes had the greatest discriminatory power relative to OS and should include examination beyond station 12 to have the greatest chance of accurate staging [20]. The findings of this study were further supported by another recent multi-institutional analysis that showed that No. 12 lymph node (36%) was the most frequent metastatic node, and the No. 8 lymph node (21%) was the second most common in patients undergoing resection of ICC. Presence of nodal metastases showed adverse long-term

oncologic impact (14 months, vs 74 months, p<0.001), and the number of LNM (0, 1-3, 4≤) was also significantly related to negative oncologic impacts in patients with resected ICC (74 months vs 19 months vs 11 months, p<0.001). Thus, surgical retrieval of ≥4 nodes was recommended in order to improve the survival outcomes in patients with ICC [21]. Similar findings emerge from the literature of other biliary cancers [22,23].

Tumor burden score in ICC

Tumor burden score (TBS) as single metric was recently shown to identify transplantable patients within and beyond Milan Criteria at higher risk of HCC recurrence [24] as well as resectable patients with Barcelona Clinic Liver Cancer (BCLC)-B stage who can benefit from surgical resection [25,26]. While TBS has been associated with outcomes among patients with HCC, its role in ICC remains poorly defined. A multi-institutional analysis showed that 5-year OS was significantly worse with higher TBS (low TBS: 48.3% vs medium TBS: 29.8% vs high TBS: 17.3%, p<0.001). Similarly, patients with low TBS had improved 5-year RFS compared with medium and high TBS patients (38.3% vs 18.7% vs 6.9%, p<0.001). While neoadjuvant chemotherapy was not associated with improved survival across the TBS subgroups, adjuvant chemotherapy was associated with increased survival among patients with high TBS (24.4% vs 13.4%, p=0.02) [27].

Preoperative laboratory values and prognosis of patients with ICC

Emerging literature supports a potential role of preoperative labs in predicting outcomes of patients with ICC undergoing resection with curative intent. Albumin-bilirubin ratio (ALBI) was recently shown to be a reliable marker of outcomes. Patients with ALBI grade 2/3 had higher odds of a prolonged length-of-stay, transfusion requirements and 90-day mortality after ICC resection. Regarding long-term outcomes, median OS worsened with increased ALBI grade: grade 1, 49.6 months vs grade 2, 29.6 months vs grade 3, 16.9 months (p<0.001). On multivariate analysis, higher ALBI grade remained associated with higher hazards of death (grade 2/3: hazard ratio=1.36, 95% CI:1.04-1.78) [28].

LabScore is a predictive model of outcomes after resection of ICC including exclusively preoperative lab values. The proposed formula is 8.2 + 1.45 × natural logarithm of carbohydrate antigen 19-9 + 0.84 × neutrophil-to-lymphocyte ratio + 0.03 × platelets - 2.83 × albumin and it is based on weighted multivariate analysis. ICC patients were classified according to the following LabScores, 0 to 9 with 54.9% 5-year OS, 10 to 19 with 38.2% and ≥20 with 21.6% (p<0.001). The model demonstrated good performance (c-index 0.70) outperformed individual laboratory markers as well as the prognostic nutritional index (c-index 0.58), and AJCC staging system (c-index 0.60) [29].

Another marker of patient baseline immune status in ICC is the systemic immune inflammation index (SII). This marker has been evaluated in multiple disease settings with contraindicatory results [30-33]. In the ICC setting, patients with high SII had worse 5-year OS (37.7% vs 46.6%, p<0.001) and cancer specific survival (46.1% vs 50.1%, p<0.001) compared with patients with low SII [34]. Overall, preoperative lab values seem to reliably predict postoperative outcomes in patients with ICC. However, advanced models are needed to incorporate laboratory, clinicopathological and tumoral biology factors to provide more accurate prediction of outcomes in resectable ICC patients.

Supporting neoadjuvant therapy in resectable ICC

There are emerging data supporting a potential role of neoadjuvant therapy in improving outcomes of patients with resectable ICC [35]. A recent multi-institutional analysis among 880 patients showed an incidence of 22.3% of very early recurrence of ICC after resection. The impact of very early recurrence on outcomes was massive since these patients had a 5-year OS of 8.9% compared to 49.8% in patients without very early recurrence (p<0.001). The development of stratification model showed that low risk patients had a 6-month RFS of 87.7% compared to high-risk patients who achieved only 49.5% 6-month RFS (p<0.001). The C-index of the model was 0.710 and generated an easy-to-use online calculator to help clinicians predict the risk of very early recurrence after curative-intent resection for ICC [36]. These results were confirmed by a recent retrospective analysis that showed that patients with stage II-III ICC, neoadjuvant chemotherapy was associated with a significantly improved OS in the propensity score-matched analysis compared to upfront surgery (p=0.02) [37]. All in all, patients at high risk should be considered for neoadjuvant therapy before resection despite their eligibility for curative-intent surgery.

Machine learning models and prognosis of patients with ICC

Currently, the performance of prognostic survival models for ICC is inadequate. A recent review compared 18 different validated prognostic models showing that only the Wang model was the sole model with good performance (C-index above 0.70) for OS. This model incorporated tumor size and number, nodal metastasis, direct invasion into surrounding tissue, VI, CA 19-9, and carcinoembryonic antigen (CEA) [38]. Artificial Intelligence has an emerging role in predicting outcomes of patients undergoing surgery for hepatobiliary malignancies [39]. Recently, the Classification and Regression Tree (CART) model was used to capture homogeneous groups of patients undergoing surgery for HCC, relative to RFS and OS [40]. The same principles were applied to patients with ICC undergoing curative-intent surgery. The model demonstrated that tumor number and size, ALBI grade and preoperative nodal (LN) status were the strongest prognostic factors associated with OS among patients undergoing resection for ICC. The model generated four distinct groups of patients with significantly different outcomes that included: a) single ICC, size≤5 cm, ALBI grade I, negative preoperative LN status; b) single tumor>5 cm or single tumor≤5 cm with ALBI grade 2/3 or single tumor≤ 5 cm with ALBI grade 1 and metastatic/suspicious LNs; c) 2-3 tumors; and d) ≥ 4 tumors. The 5-year OS among groups was 60.5%, 35.8%, 27.5%, and 3.8%, respectively (p<0.001). Similarly, 5-year RFS was 47%, 27.2%, 6.8%, and 0%, respectively (p<0.001) [41]. Another machine learning analysis showed that distinct groups of patients with ICC can have significantly different outcomes based on the size and the tumoral behavior reflected by lab values. The most common group of clustered patients included individuals who had a small-size ICC (median 4.6 cm) and median CA 19-9 and neutrophil-to-lymphocyte ratio (NLR) levels of 40.3 UI/mL and 2.6, respectively. Another group consisted of patients who had larger-size tumors (median 9.0 cm), higher CA19-9 levels (median 72.0 UI/mL), and similar NLR (median 2.7). The least common phenotype of ICC patients included medium-size ICC (median 6.2 cm), the lowest range of CA19-9 (median 26.2 UI/mL), and the highest NLR (median 13.5) (all p<0.05). Median OS worsened incrementally among the three different clusters (Cluster 1 vs 2 vs 3; 60.4 months (vs 27.2 months vs 13.3 months, p<0.001) [42]. Similar findings are supported by a recent model that included 6 independent prognosis factors such as CEA, Ca 19-9, alpha-fetoprotein, prealbumin, T and N of ICC staging category in the 8th edition of AJCC. The proposed scoring system showed a more favorable discriminatory ability and model performance than the AJCC 8th with a higher C-index of 0.693 [43]. The overall impression is that the machine learning can efficiently guide the decision-making process in patients with resectable ICC.

Transplant oncology and ICC

Since the introduction of the Milan Criteria, the field of transplant oncology has emerged with an increasing proportion of liver transplants being performed for oncological indications [44-49]. Significant improvements have been made in RFS and OS for selected patients with HCC, hilar cholangiocarcinoma, neuroendocrine tumors and colorectal liver metastases [44-47]. Recent data support a potential role of transplantation in patients with ICC. Systematically reviewed literature reports a 50-73% for those patients with exclusively ICC on explant pathology whereas larger tumors (>2cm) were related to worse 5-year OS of 40%. Interestingly, this tumor size (>2 cm) and multifocality risk factors for tumor recurrence and worse outcomes when compared with similar HCCs with similar characteristics. However, patients with small single tumors had similar results to those of patients with HCC [49,50]. These promising results suggest that patients with very early ICC should perhaps be considered as a formal indication for LT.

Conclusions

Surgical management of ICC is challenging due to high incidence of recurrence and controversies around the management of nodal disease. Most of current staging and predicting models are inadequate in predicting outcomes of patients with resectable disease. Most of them are actually failing in identifying patients with early recurrence potential who might benefit from alternative management strategies including neoadjuvant chemotherapy. Also, more research is needed towards the direction of the role of liver transplantation in patients with ICC.

Conflict of interests

The author declares no conflict of interests.

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