

# Intrahepatic cholangiocarcinoma, are we making progress?

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There is a worldwide increase in the annual incidence of intrahepatic cholangiocarcinoma (iCCA) (1). For this reason, the review from Bupathi *et al.* assesses a highly relevant topic. Their work shows several important advances in the management of iCCA in the past few decades (2). They review the role of adjuvant therapy for patients with early stages and adverse prognostic factors (i.e., lymph nodal disease). Also, they report recent achievements in the management of advanced disease. Despite the progress made in the management of iCCA, much is still to be done.

Given there is no curative treatment option for advanced iCCA and patients with very-early iCCA ( $\leq 2$  cm) may achieve better survivals, the keystone for a good success remains on the early diagnosis (3). In this regard, patients with higher risk for primary liver cancer, such as patients with primary sclerosing cholangitis or patients with chronic hepatitis should be subject of surveillance programs (4). On the other hand, many patients with iCCA are still misdiagnosed as hepatocellular carcinoma (HCC) so there is an urgent need to improve the non-invasive techniques to diagnose this cancer in patients with liver disease. Moreover, there is a lack of biomarkers to help in the early detection of this disease. On this subject, carbohydrate antigen (CA) 19-9 has a low sensitivity and specificity for early detection (62% and 63%, respectively) (3). Thus, the development of novel biomarkers for iCCA diagnosis should be a focus of investigation.

Liver resection (LR) continues to be the main curative option for resectable iCCA. Unfortunately, only 20–40% of patients diagnosed with iCCA will be deemed candidates for surgical resection (3), being the main caveat for this

approach the remnant liver volume and the degree of underlying liver disease. In a multicentric retrospective study, the median survival after LR was 39 months and the 5-year actuarial survival was 40% (5). To expand the option of LR to more patients, techniques to improve the hepatic compensatory regeneration after portal vein embolization have shown encouraging results. The use of yttrium-90 (Y90) labeled microspheres (also called “radiation hepatectomy”) has been proven safe and effective to increase the liver remnant volume while treating the cancer (6). In 2013, Vouche *et al.* published a cohort of 83 patients with “unresectable” liver cancers (67 HCC, 8 colorectal metastases and 8 iCCA) who were treated with Y90 radioembolization. They showed results related to lobar hypertrophy. Thereafter, 11 patients were converted to surgical therapies (5 underwent LR and 6 underwent LT). Their work shows that Y90 might be an option as bridge to resection for liver cancer patients (7). A phase III trial comparing Y90 + gemcitabine/cisplatin compared to gemcitabine/cisplatin in advanced iCCA is currently accruing (8). This trial will elucidate the effect of Y90 in iCCA compared to standard of care chemotherapy. Interestingly, one of the secondary outcomes of this trial is downstaging to surgery.

To date, the proportion of patients diagnosed of iCCA recurrence after LR remains high. Hyder *et al.* have reported a recurrence rate of 53% after a median follow-up of 31 months following LR (9). The most frequent site of iCCA recurrence was intrahepatic [98/161 (61%) of recurrences]. Patients with a tumor size  $\geq 5$  cm had a median recurrence-free survival of 17 months, whereas patients

with iCCA <5 cm had a median recurrence-free survival of 41 months ( $P<0.001$ ). These findings may stress out the relevance of the pro-carcinogenic hepatic environment in the genesis of recurrence and the importance of early detection of iCCA. As Bupathi *et al.* have well pointed in their review article, there is a lack of prospective trials supporting the use of adjuvant chemotherapy after LR for iCCA (2). The BILCAP trial was presented recently at the American Society of Clinical Oncology meeting showing encouraging results of capecitabine as adjuvant therapy for biliary cancers (10). All biliary cancers were analyzed together. It is known that iCCA has a different molecular pathogenesis than other biliary cancers (3). Nevertheless, at our Institution we have adopted this and patients undergoing resection of iCCA are being treated with capecitabine as adjuvant therapy in a case-by-case basis. Further development of standardized adjuvant protocols aiming to decrease the incidence of iCCA recurrence will necessarily go through iCCA-specific prospective trials.

There has been recent encouraging studies suggesting that patients with non-resectable iCCA might be potential candidates for liver transplantation (LT) (11). Nevertheless, LT as a treatment option for non-resectable iCCA is still controversial, mainly due the lack of prospective studies. LT has several potential advantages for patients with iCCA. In cases where the tumor is restricted to the liver and the LR is not an option (i.e., patients with advanced cirrhosis), a total hepatectomy would offer a complete resection of all evident disease and the pro-oncogenic hepatic environment. In a multicentric retrospective study, we demonstrated that patients with very-early ( $\leq 2$  cm) iCCA who underwent LT had better survival when compared to patients with more advanced disease (12). These results were validated in a multicentric study that assessed the post-LT outcomes for cirrhotic patients that were found to have iCCA in the explant pathology. Those patients with very-early iCCA had a 5-year actuarial survival of 65%, whereas patients with single tumors >2 cm or multifocal iCCA had a 5-year actuarial survival of 18% ( $P=0.02$ ) (13). This study provides supports the use of LT for cirrhotic patients with a single iCCA tumor  $\leq 2$  cm. Indeed, this may represent the best and sole treatment option for these patients. On the other hand, the option of LT for non-resectable very early iCCA, given the current organ shortage, could rise concerns regarding the increase in the number of potential patients on liver transplant waiting lists. To address this, the use of live donor liver transplantation (LDLT) may be an option for non-resectable iCCA. LDLT offers a unique source of liver

grafts different to the deceased donor pool. This potential increase in the grafts source has led to an expansion in the LT criteria for hepatocellular carcinoma, mainly in Asian centers (14). Future studies should focus on criteria for patient selection for LT for non-resectable iCCA.

In summary, progress has been made in the treatment of iCCA yet much needs to be done. Surgical resection is still the main treatment option for iCCA. To improve the outcomes, the next steps in the development of iCCA treatment should be: standardization of adjuvant therapies after LR, strategies to expand resectability and the potential role of LT for the treatment of iCCA. Further prospective studies should focus on these questions in order to provide better care for patients with iCCA.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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