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EDITORIAL

# Consensus Conference on Hilar Cholangiocarcinoma

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The Consensus Conference on the Multidisciplinary Management of Hilar Cholangiocarcinoma represents a serious effort to assess critically the current landscape and evidence for the diagnosis and management of hilar cholangiocarcinoma (HCCA). While the authors are in general agreement with the consensus statements, they have also identified a few controversial areas that require further investigation.

Patients with HCCA face many hurdles in receiving effective therapy. The disease is rare, and most patients do not have any of the specific risk factors, making screening ineffective. The early symptoms are often non-specific, and most patients are not resectable when jaundice develops and the ultimate diagnosis is made. Tumour markers (CA 19-9) are inaccurate, particularly in the setting of jaundice. Surgery remains the only known curative therapy, but the tendency towards the early invasion of lymphatics, blood vessels and adjacent structures make resection complex and often unsuccessful. Nonetheless, as this consensus statement points out, a systematic and consensus-driven approach provides the best opportunity for patients to receive the most effective care.

While many patients may have a prodrome of weight loss and other non-specific symptoms jaundice usually leads patients to seek medical attention. Cross-sectional imaging reveals the presence of intrahepatic biliary dilation. Ideally, as this consensus conference points out, a high-quality helical multi-slice CT scan with intravenous contrast and appropriately timed scans remains the best single test to identify and stage the tumour. The accuracy of a computed tomography (CT) scan is degraded in the presence of a biliary stent. Unfortunately, in most referral centers' experience, patients do not receive the most effective imaging test and are stented prior to referral. This makes subsequent staging less accurate and represents an opportunity to improve the care for these patients during the initial evaluation. MRI with MRCP provides additional information on the extent of biliary involvement. ERCP is of relatively low yield in these patients, with very poor rates of diagnosis by endobiliary cytology, even with the use of additional techniques like FISH. Also, endoscopic stenting of complex hilar strictures is challenging and usually involves multiple very small caliber stents. As the consensus statement points out, percutaneous drain placement is usually superior to endoscopic stenting in these patients. In many patients, EUS-guided FNA of strictures or nodes is also a reasonable choice to obtain a tissue diagnosis. The consensus conference makes a very important point; pathological confirmation is not required prior to surgical resection. It is, however, quite important that benign causes including IgG4-related biliary strictures, benign strictures due to Mirrizi's syndrome, primary sclerosing cholangitis, or previous biliary surgery are considered prior to surgery in patients without a tissue diagnosis. If ERCP is performed, the biliary cytology should be subjected to FISH analysis. Endobiliary forceps biopsy and cholangioscopy-directed biopsy should be considered if feasible, as these techniques add to the diagnostic yield.

Initial staging of HCC is designed to identify those patients in whom surgery is most likely to be successful. In the consensus statement authors describe the essential features that must be assessed, including the extent of the primary tumour, vascular involvement, residual liver volume and function, the presence of nodal or distant metastases, and the patient's ability to tolerate surgery. Of particular note from the conference, FDG-PET is not recommended as a routine staging procedure.

A resection with negative margins is associated with better chances of survival for patients presenting with HCCA. The authors have emphasized the benefits of adding liver parenchyma and caudate lobe resection. We support that strategy in light of the improved survival associated with the more aggressive surgical approach.[1] Some patients will need a multimodality strategy to achieve an adequate future liver remnant volume, before attempting any surgical resection. This disease should be treated in the setting of a tertiary medical centre given its complexity. The use of portal vein embolization may add safety

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for HCCA patients when liver parenchyma hypertrophy is required. Portal vein embolization has been shown to be a safe and effective procedure, even in the setting of biliary stenting.[2] These strategies of complex pre-operative optimization support the assertion that this disease is best treated in experienced referral centres.

A careful review of good quality cross-section imaging, as well as the patient performance status, will lead to better surgical results, with the observation that the choice for using high-quality CT or MRI should be based on local expertise. A routine frozen section to evaluate margins is still a matter of debate, and should be considered in order to achieve better quality control of the procedure as well as a potential survival benefit.[3] We believe this should be addressed in future studies.

As previously mentioned, patients are often stented before any surgical consultation. Although the indications and methods of biliary decompression have been controversial after the Japanese report of increased incidence of seeding associated with percutaneous trans-hepatic cholangiogram, the experience with endoscopic naso-biliary drainage has not been reproduced in Western centres.[4] We agree that the use of PTC remains standard. The number of drains and location should be made in a 'case-by-case' basis and discussed with the surgical team before any attempt at biliary manipulation.

The role of liver transplantation in this disease is clear. A liver transplant should be the procedure of choice in patients with primary sclerosing cholangitis (PSC). The experience from North American centres demonstrates the impact that multimodality pre-transplant treatment may offer. The improved survival of patients with incidentally discovered tumours in the setting of PSC after an induction multimodality protocol suggests an opportunity for clinical investigation of multimodality therapy for patients with *de novo* HCCA. For patients with unresectable *de novo* HCCA, multimodality therapy followed by liver transplantation may be a promising opportunity. Induction therapy followed by a liver transplant should be performed under controlled protocols owing to the limitations of graft availability and the costs of this treatment plan. As the results from these experiences are published, we hope to see generalizable, promising outcomes duplicated at multiple centres.

The authors have not included recommendations regarding a regional lymphadenectomy. Although the therapeutic impact of this procedure is controversial, nodal disease burden does represent an important predictor of survival. Efforts should be made to determine the ideal number, and location of lymph nodes harvested. The importance of this aspect of a resection is supported by the inclusion of nodal status in modern staging systems.

Despite the availability of curative treatment modalities including surgical resection and liver transplantation, most patients with HCCA will present with recurrent, locally advanced, or metastatic disease with a poor prognosis. While chemotherapy and radiation have been used extensively either alone or in combination, there is a paucity of level one evidence with well-conducted clinical trials assessing the value of these treatment modalities in well-defined clinical settings.

As outlined in the Consensus Statements, based on the results of a phase III trial (ABC-02) with improved survival benefits, the combination of gemcitabine and cisplatin has become the standard therapy for patients with advanced and metastatic HCCA.[5] However, it is worth noting that even with the combination chemotherapy, the median survival for patients with advanced biliary tract cancers remains < 1 year, highlighting the unmet need for more effective systemic therapy. Of the 410 patients enrolled in the ABC-02 trial, only 57 patients had HCCA and the hazard ratio for this subgroup was 0.59 (0.32–1.09). Therefore, there is a need to enrich the experience of a combination chemotherapy regimen in HCCA. While molecularly targeted therapy holds promise to improve the outcome for patients with HCCA, there are currently no approved targeted therapies in cholangiocarcinoma. Moreover, recent efforts with targeted and whole exome sequencing have identified actionable genetic signatures in intrahepatic chlangiocarcinoma (ICC) including mutations in the metabolic genes isocitrate dehydrogenase (IDH) 1 and 2 and translocations involving the fibroblast growth factor receptor 2 (*FGFR2)* gene.[6–9] No clear, actionable genetic signatures have been identified in HCCA.

For patients who have undergone an R0 resection for HCCA, there is no standard adjuvant therapy. However, three ongoing randomized phase III trials are assessing the value of various chemotherapy regimens including capecitabine, gemcitabine-oxaliplatin and gemcitabine-cisplatin in patients undergoing macroscopically complete surgical resection for biliary tract cancers including HCCA.[10] The role of adjuvant chemoradiation is being assessed in the ongoing Southwest Oncology Group 0809 study, which is a single-arm phase II trial of post-operative gemcitabine-capecitabine based chemotherapy followed by chemoradiation for resected cholangiocarcinoma and gall bladder tumours. Based on the pattern of recurrence for HCCA, for margin-positive or node-positive resected HCCA, chemoradiation or chemotherapy should be considered. In this setting, the role of chemotherapy and the sequence of chemotherapy and chemoradiation remain to be defined in prospective clinical trials.

For patients who present with unresectable HCCA, either chemotherapy with gemcitabine/cisplatin or chemoradiation should be considered as treatment options (ref NCCN). The role of intraluminal brachtherapy remains to be defined. For patients who present with local recurrence with HCCA, chemotherapy is preferred, and radiation should be considered only in selective settings given the known toxicity risks inherent to radiation delivery to the jejunal anastomosis.

In summary, while combination chemotherapy with gemcitabine–cisplatin is the current standard therapy for patients

with metastatic HCCA, the role of chemoradiation or chemotherapy in the adjuvant setting, in patients with unresectable or recurrent disease remains to be defined in carefully designed prospective clinical trials.

## References


1. Burke EC, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. (1998) Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 228:385–394.
2. Palavecino M, Abdalla EK, Madoff DC, Vauthey JN. (2009) Portal vein embolization in hilar cholangiocarcinoma. *Surg Oncol Clin N Am* 18:257–267, viii.
3. Ribero D, Amisano M, Lo Tesoriere R, Rosso S, Ferrero A, Capussotti L. (2011) Additional resection of an intraoperative margin-positive proximal bile duct improves survival in patients with hilar cholangiocarcinoma. *Ann Surg* 254:776–781, discussion 81–3.
4. Takahashi Y, Nagino M, Nishio H, Ebata T, Igami T, Nimura Y. (2010) Percutaneous transhepatic biliary drainage catheter tract recurrence in cholangiocarcinoma. *Br J Surg* 97:1860–1866.
5. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A *et al.* (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 362:1273–1281.
6. Wang P, Dong Q, Zhang C, Kuan PF, Liu Y, Jeck WR *et al.* (2013) Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hypermethylation targets with glioblastomas. *Oncogene* 32:3091–3100.
7. Jiao Y, Pawlik TM, Anders RA, Selaru FM, Streppel MM, Lucas DJ *et al.* (2013) Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. *Nat Genet* 45:1470–1473.
8. Graham RP, Barr Fritcher EG, Pestova E, Schulz J, Sitailo LA, Vasmatzis G *et al.* (2014) Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. *Hum Pathol* 45:1630–1638.
9. Sia D, Losic B, Moeini A, Cabellos L, Hao K, Revill K *et al.* (2015) Massive parallel sequencing uncovers actionable FGFR2-PPHLN1 fusion and ARAF mutations in intrahepatic cholangiocarcinoma. *Nat Commun* 6:6087.
10. Zhu AX. (2015) Future directions in the treatment of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* 29:355–361.