Editorial Commentary

Primary sclerosing cholangitis and cholangiocarcinoma: the 2023 practice guidance and future perspectives

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The 2023 practice guidance on primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA) of the American Association for the Study of Liver Diseases (AASLD) came as a needful update to the previous 2010 guidelines on PSC, with a first-time inclusion of dedicated guidance on the diagnosis and management of CCA (1,2). This data-supported approach developed by consensus of an expert panel, provides guidance statements based on analytical review of the relevant literature. The production of guidance rather than guidelines relates to the paucity of sufficient randomized controlled trials suitable for systematic review and meta-analysis (1). The publication is comprehensive, illustrative of remarkable progress since the 2010 guidelines, and will be a useful tool in providing high-quality care for these patient groups. Aside from the significant amount of new information and helpful recommendations, there is room to identify current gaps and future directions.

The new terminology and clarifications about biliary strictures in PSC, including dominant, high-grade and relevant stricture, are valuable as they cover pre-existing gaps while promoting the use of a common language worldwide, as recently recommended by the International PSC Study Group (1,3). High-quality MRCP is recommended as the gold standard for diagnosis, while avoiding ERCP for diagnostic purposes is highlighted, owing to the increased risk of complications. The recently published guidelines of the European Association for the Study of the Liver (EASL) are less stringent on this matter but in agreement that MRCP is the preferred diagnostic tool (4).

While liver biopsy is fundamental to confirm a diagnosis of small-duct PSC or autoimmune hepatitis overlap (3), it is not recommended for fibrosis staging in clinical practice (1,4). However, the role of liver histology in PSC has been recently revisited and is now considered essential in the regulatory approval process for new therapeutic strategies (5). In the current landscape of intense development of surrogates of clinical endpoints, it is worth mentioning the recent data on collagen proportionate area (CPA), a quantitative method to measure the proportion of fibrosis on liver biopsy samples using digital image analysis. Further to the traditional

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histology scores, CPA provides useful information for risk-stratification and prognostication in PSC, and may be particularly useful in the clinical trials setting, for assessment of response-to-treatment and regression of fibrosis (6).

The utility of liver stiffness assessment by transient elastography or magnetic resonance elastography to estimate liver fibrosis and predict clinical outcomes, is increasingly recognised (4,7). Albeit not discussed in the new guidance, increasing evidence shows that the more recently developed elastographic techniques such as point- and 2D-/3D-shear wave elastography can be reliable for assessment of liver fibrosis and risk-stratification in PSC. Recent data on spleen stiffness as a predictor of presence of oesophageal varices in PSC are also encouraging (8).

Clinical prediction scores designed for PSC do not have generalised reliability and applicability; the 2023 practice guidance provides a useful diagram to guide the clinician in choosing, based on individual features (1).

Recommendations on the use of ursodeoxycholic acid (UDCA) in PSC have been inconsistent over time, and its potential to improve clinical outcomes remains unclear. However, a moderate dose of UDCA is now suggested as a possible treatment for patients not interested in or ineligible for clinical trials, since it may improve serum liver tests and surrogate markers of prognosis. The suggested dose, however, differs between the AASLD guidance (13–23 mg/kg/day) and the recent EASL guidelines (15–20 mg/kg/day) (1,4). As controversy still exists on the topic, further data is required to establish optimal doses.

The 2023 AASLD guidance enumerates various pharmacological treatments currently investigated in clinical trials. It is worth also noting that faecal microbiota transplant has shown good safety profile and some preliminary efficacy signals in a recent pilot study, and is currently being further investigated (9).

The new guidance is the first ever to recommend the onset of colorectal cancer surveillance in patients with inflammatory bowel disease at the age of 15 years (1). Notably, it recommends considering cholecystectomy for gallbladder polyps >8 mm, in contrast with the European guidelines from 2017, which suggested a cut-off size of >6 mm (10), while the EASL guidelines recommend it for polyps ≥8 mm (4). Furthermore, EASL suggests assessment of smaller polyps with contrast-enhanced ultrasound, and consideration of cholecystectomy if they enhance (4).

The new guidance appropriately differentiates *de novo* CCA and PSC-associated CCA, which owing to distinctive features should be seen indeed as different entities (11).

The provided diagnostic algorithm for relevant strictures in PSC is highly useful (1). Some aspects are particularly interesting, including initial suspicious cytology warranting ERCP in 3 months, regardless of fluorescent in situ hybridization (FISH) results (1). It would be useful to assess the proportion of PSC patients ultimately diagnosed with CCA after recommended interval ERCP at 3 months and, subsequently, the proportion of those eligible for curative-intent treatment. Furthermore, clear recommendations are warranted for when initial negative/suspicious cytology with FISH polysomy is followed by ERCP revealing suspicious cytology with either FISH polysomy or negativity. Importantly, AASLD recommends that FISH should be obtained in all patients with suspected perihilar CCA (pCCA) or distal CCA (dCCA) (1). While FISH has undoubtedly increased the diagnostic accuracy of biliary brushings cytology, it is not uniformly available for this purpose, including in prominent centres. It has to be underlined that the ongoing progress with liquid biopsies in different fronts, including diagnosis (12), might result in the inclusion of this technique in future guidance and at various stages within the diagnostic algorithms.

A few remarks on the valuable therapeutic algorithms for the three topographic categories of CCA can be drawn. A guidance statement explains that for unresectable liver-limited intrahepatic CCA (iCCA) orthotopic liver transplantation (OLT) should be considered under research protocols only (1), while the schematic therapeutic algorithm recommends referral to a liver transplant centre for unresectable iCCA ≤2 cm. Although iCCA is still largely considered a contraindication for OLT, recent promising outcomes have led to the consensus statement recommendation by the European Network for the study of CCA that OLT should be considered as a potentially curative option especially in patients with very early stage unresectable iCCA (≤2 cm) and cirrhosis (13).

The guidance recommendation for resectable pCCA is "surgery followed by adjuvant chemotherapy". Notably, in PSC-associated pCCA, surgical resection is most frequently precluded owing to various parameters including a higher rate of multifocal CCA, skip cancer lesions, poor quality of the liver parenchyma and hepatic dysfunction with reduced regenerative capacity (11,13). In contrast, the option of neoadjuvant chemoradiotherapy followed by OLT is increasingly being recognised as the optimal treatment strategy and remains among the inclusion criteria of the Mayo Clinic protocol. The outcomes are superior compared

to *de novo* pCCA (11,13), likely due to earlier detection in PSC owing to routine surveillance (1) and a possible higher responsiveness to radiation therapy on a background of PSC (11,13). Extension into the distal bile duct is an established reason for consideration of combined OLT and pancreatoduodenectomy (11,13). The emphasis of the AASLD group on the Mayo Clinic protocolised approach to early pCCA is important, particularly as OLT for pCCA remains contraindicated in many countries despite the evidence of very good outcomes, on the background of the relative scarcity of donor organs.

The TRANSPHIL trial (NCT02232932), a French prospective open-label randomised multicentre comparative study ongoing since 2012, is aiming to clarify whether the best treatment for resectable pCCA is neoadjuvant chemoradiotherapy followed by OLT or standard of care liver and bile duct resection. Should previous positive outcomes in favour of OLT be confirmed, this will lead to a true paradigm shift in the management of pCCA (11). Notably, the trial lists PSC among the exclusion criteria for enrolment.

Even without a statement regarding the role of lymphadenectomy, the practice guidance discusses that for iCCA in general, surgery involves liver resection and portal lymphadenectomy (1). This approach is not uniformly accepted and the role of lymphadenectomy in this setting as a standard part of the surgical resection is under ongoing debate. Our recent meta-analysis showed that lymphadenectomy did not improve overall and disease-free survival, except in Japanese studies. However, lymph node metastases were found in 27.7% of patients undergoing lymphadenectomy, suggesting that it may aid in adequate staging (14). Statements regarding the adequacy of lymphadenectomy in pCCA and dCCA are lacking. There is controversy on the matter in pCCA, with no established minimal number of harvested lymph nodes for histopathological assessment, while for dCCA, a minimum of 12 lymph nodes has been suggested as appropriate for accurate staging (15). Firmer recommendations are anticipated in the future on this topic.

When CCA extends both distally and towards the liver, attempts at hepatopancreatoduodenectomy have been challenging with high perioperative morbidity and mortality (97.4% and 26%, respectively, in recent series) and 5-year overall survival of 17.9–49.2% (13). Accordingly, this procedure may be suitable to consider as a potentially curative approach only in very carefully selected fit patients.

As underlined by the 2023 guidance, laparoscopic liver surgery is a safe approach for liver cancer (1). Notably, the rapid accumulation of evidence with robotic surgery may soon define its place in the treatment of iCCA.

In summary, the new AASLD practice guidance on PSC and CCA came at a suitable time and, compared with the guidelines from 2010, is highly indicative of the remarkable progresses made in understanding these diseases and their management. While it is expected to function as a valuable tool for specialists in the relevant fields, the current pace of progress is promising that further important outstanding questions may be answered in the near future.

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