

# Recommendations on Perihilar Cholangiocarcinoma

## The Milan Jury-based Consensus

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 On behalf of the Consensus4pCCA Collaborative

**Objective:** To establish comprehensive recommendations on the management of perihilar cholangiocarcinoma (pCCA) and to identify areas in need of future investigation.

**Background:** The lack of consensus in management of pCCA across institutions worldwide impairs optimal patient care and best-achievable oncological outcome. A holistic and critical assessment of the body of evidence and collaborative guidance are required.

**Methods:** The Consensus4pCCA conference developed unbiased consensus using the Zurich-Danish model. An impartial and multidisciplinary jury adopted comprehensive recommendations

grounded on the work of 8 expert panels answering predefined clinical questions and considering the best-quality evidence through a systematic review. The development of recommendations complied with GRADE and SIGN50 methodologies.

**Results:** Seventy-one international experts considered 570 studies. Ten jury members concluded 71 recommendations covering definition and diagnosis, preoperative assessment and optimization, surgical resection, liver transplantation, and outcome reporting for pCCA patients. The consensus underscored that making patients amenable to high-quality curative resection and reducing its associated morbidity must be of highest priority. As such, multidisciplinary expertise and centralized care at all stages of disease management are critical to ensure both safety and oncological adequacy. To overcome the evidence gap for rare diseases like pCCA, the jury urged large-scale registries to address open questions across the disease continuum and highlighted priorities for future investigation.

**Conclusion:** The Consensus4pCCA represents an unprecedented commitment to collectively harmonize global treatment strategies for pCCA. This collective effort bridges the gap between expert opinions and clinical evidence and holds great promise to improve patient outcomes in the future.

**Key Words:** biliary drainage, chemotherapy, consensus, liver hypertrophy, liver transplantation, perihilar cholangiocarcinoma, recommendations, resectability, Zurich-Danish model

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M.P. and F.R.: contributed to the literature review group. G.J.G., M.L., L.C., T.E., V.A., J.W.V., J.K.H., and C.B.: expert panel chairs. J.B.: jury president.

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Perihilar cholangiocarcinoma (pCCA) remains one of the most challenging malignant tumors, with many gray areas and a lack of consensus on many aspects across institutions. Most patients with pCCA face a dismal prognosis, with only a minority amenable to a surgical resection, which remains the only chance for cure. Even in the best-case scenario, that is, benchmark patients operated at expert centers, the 5-year overall survival (OS) does not exceed 40%. In addition, surgery remains one of the most demanding procedures associated with up to 70% severe ( $\geq$  grade 3<sup>1</sup>) complications, and a 90-day mortality reaching 13%, even in a benchmark setting.<sup>2,3</sup> For example, one in every fifth patient needs a relaparotomy in the postoperative course.<sup>2</sup> On top of these distressing figures, only two-thirds of patients undergoing radical surgery may benefit from negative resection margins, one of the key predictors for long-term oncological outcome.<sup>2</sup> On a positive note, recent

data suggest that liver transplantation (LT) may offer an alternative in pushing the boundaries of resectability, but this approach is restricted to only highly selected patients.<sup>4,5</sup> The potential benefits of neoadjuvant chemo-immunotherapy in expanding resectability and improving survival outcomes remain unclear.

There is also a lack of consensus in almost every area of pCCA including disease staging, resectability criteria<sup>6-8</sup> and perioperative practices,<sup>9</sup> and the absence of guidelines for therapy-decision making is a gap that still needs to be fully addressed.<sup>10-14</sup> Even the route and timing of biliary drainage in these cholestatic patients remain controversial, leading to suboptimal initial management at nonexpert centers with irreversibly impaired outcomes.<sup>9</sup> Therefore, a holistic and critical assessment of the body of evidence and preferred management strategies is urgently required.

The Consensus4pCCA initiative aimed at developing impartial recommendations to provide comprehensive, evidence-based guidance on the multidisciplinary management of pCCA. The focus was essentially on perioperative diagnostic and therapeutic pathways, surgical procedures including liver transplantation, and the evaluation of relevant outcomes and metrics to compare treatment strategies. Importantly, the initiative sought to pinpoint areas in need of future investigation.

## METHODS

### The Zurich-Danish Model

Consensus development adhered to the Zurich-Danish format<sup>15-18</sup> (Fig. 1). This validated, evidence-based model is structured in 3 phases: (1) preparation, (2) consensus meeting, (3) jury deliberations. Aiming at producing unbiased recommendations, this approach strictly separates the responsibilities of different stakeholders: Experts in the field were given the task to critically assess and condense best-quality evidence, the public audience engaged in on-site meeting discussions challenging the experts' conclusions, and the impartial jury was entrusted with formulating and adopting the final recommendations.

1. The preparation phase encompassed drafting clinical questions, a comprehensive literature review, and a first proposal of recommendations by an international group of experts in the field. Under the guidance of the steering committee, the local organizing committee (LOC) defined 8 panels, each addressing different topics in the

management of pCCA. Panel experts then answered 5 to 7 core clinical questions per panel based on best-quality evidence.

2. The consensus meeting was carried out in Milan on December 5-6, 2024. The designated expert panel chairs presented their respective recommendations along with the supporting evidence-based rationale. Each presentation was followed by open discussions, initially led by the jury, and subsequently extended to the public.
3. Each meeting day was directly followed by closed jury deliberations with the option to summon expert panel chairs for further inquiries. In a concluding closed session, the jury finalized and adopted the final recommendations based on the GRADE approach.<sup>19-21</sup>

### Recruitment of Experts and the Jury

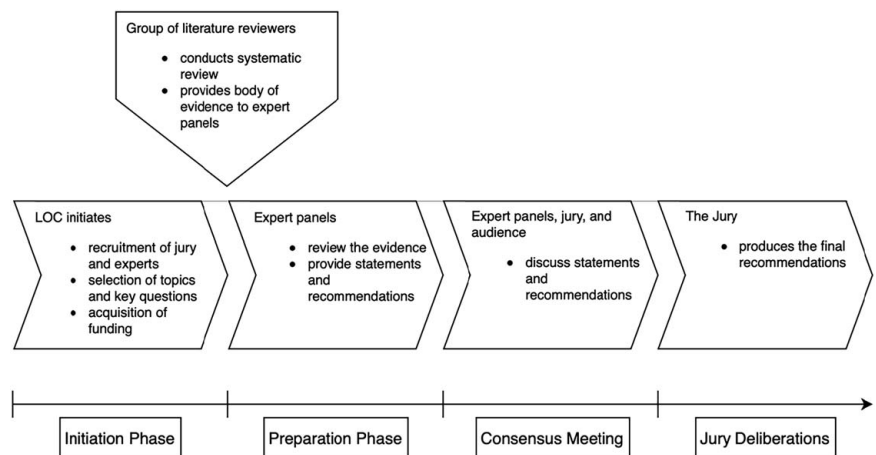
Members of the steering committee and panel experts were selected based on their subject matter expertise, defined by one or more of the following criteria: (i) an academic track record as senior author of landmark publications in the field, (ii) exceptional clinical expertise in the management of the disease, or (iii) representation of cholangiocarcinoma patient organizations. The group of experts comprised all different stakeholders involved in pCCA management, that is, hepato-pancreato-biliary surgeons, liver transplant surgeons, hepatologists, gastroenterologists, interventional radiologists, oncologists, and pathologists, while maintaining a demographical and geographical balance.

The jury consisted of ten members, including hepatologists, non-hepato-pancreato-biliary surgeons, epidemiologists, and bioethicists, none of whom were directly involved in the management of pCCA patients or research in the field to avoid bias (Table 1). In addition, members were selected based on their expertise and previous involvement in consensus meetings and familiarity with the process of guideline development. The jury was required to ensure equitable geographic representation across 3 continents.

### Panels and Clinical Questions

Each panel was assigned to answer 5 to 7 core clinical questions, aimed at covering the main aspects in the management of pCCA (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>). The questions were drafted by the LOC and reviewed and approved by the steering committee before their submission

**FIGURE 1.** The Zurich-Danish format is used to develop unbiased recommendations in medico-surgical practice (modified with permission from Lesurtel et al<sup>15</sup> and Hobeika et al<sup>18</sup>). Abbreviations: LOC (Local Organizing Committee)



**TABLE 1.** Jury Composition

Jordi Bruix*	Hepatologist	Spain
Robert Caiazzo	Surgeon	France
Nicolò de Manzini	Surgeon	Italy
Cesar Hincapié	Epidemiologist	Switzerland
Arnulf Hoelscher	Surgeon	Germany
Samia Hurst	Bioethicist	Switzerland
Matteo Iannaccone	Immunologist	Italy
Lawrence Kim	Surgeon	USA
Takeshi Sano	Surgeon	Japan
Pierpaolo Sileri	Surgeon	Italy

\*Jury president.

to panel experts. A chair for each panel was defined by the LOC, with the main task to organize panel work. Panel 1 and 2 focused on questions related to the definition and diagnosis including preoperative assessment of pCCA, panel 3 evaluated preoperative optimization (including biliary drainage and techniques for liver hypertrophy), panel 4 specifically answered surgery-related questions, panel 5 and 8 focused on postoperative outcome measures, panel 6 on perioperative oncological treatments, and panel 7 covered the topic of transplantation.

### Systematic Literature Review

The body of evidence was assessed by a dedicated group of 17 literature reviewers consisting of hepatopancreato-biliary and transplant fellows, surgeons, and research fellows. The systematic literature review adhered to the SIGN50 guidelines of guideline development,<sup>22</sup> the search encompassed the 3 databases Embase, Medline, and Cochrane (Supplemental Table 2, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>). Original articles on any aspect of pCCA management with available full text published in English from January 2000 to March 2024 were eligible for inclusion. Case reports, noncomparative studies with <10 reported cases, and nonoriginal studies were excluded (Supplemental Table 3, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>). Title/abstract screening, full text screening, data extraction, and critical appraisal of the quality of evidence were performed by 2 independent and blinded reviewers (Supplemental Figure 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>). Conflicts were resolved by a third independent reviewer. Studies were assessed for their relevance to any of the panels and categorized according to the PICO framework.<sup>23</sup> Each study was considered of either *high*, *acceptable*, *low*, or *unacceptable* quality. Studies of *unacceptable* quality were categorically excluded; studies of *low* quality were included only if no higher quality evidence was available. A summary database of all studies was provided to the panel experts before the consensus meeting. Panel experts expanded the search until November 2024.

### Level of Evidence and Strength of Recommendations

Each recommendation was assigned a level of evidence (levels 1–5) using the GRADE approach<sup>19–21</sup> based on the highest quality study available. Recommendations were graded as either *STRONG* or *WEAK*. The jury also had the option to give no recommendation for a given topic or question when they felt a recommendation was too speculative or determination of direction of a recommendation was not possible. Factors considered for determining

direction and strength of recommendations included certainty of evidence, balance between desirable and undesirable effects, confidence in the magnitude of effect, values and preferences and their variability, ethical obligations, feasibility, and resource use.<sup>19–21</sup>

## RECOMMENDATIONS

### Literature Review and Consensus Conference

A total of 570 articles were considered for the consensus development (Supplemental Figure 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>); half of which were published over the last 5 years (n = 288, 49.5%). Most studies were of an observational nature (n = 479, 84%) and deemed of acceptable quality (n = 476, 83.5%). While half of the studies investigated different aspects of surgical resection (n = 299, 52.5%), 20.4% (n = 116) reported on diagnostic and staging modalities, 12.5% (n = 71) on perioperative management and liver augmentation techniques, 5.6% (n = 32) on systemic and loco-regional therapies, and 5.6% (n = 32) on liver transplantation.

The panels consisted of 71 dedicated experts spanning Europe (n = 40, 56.3%), North America (n = 17, 23.9%), Asia (n = 12, 16.9%), and South America (n = 2, 2.8%). The audience at the consensus meeting comprised a total of 226 on-site attendees. The entire Consensus4pCCA Collaborative is listed in Supplemental Table 4, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>.

### Panel 1. Definition and Diagnosis

#### Definition

Experts and the jury agreed on the anatomic definition of pCCA as the primary biliary tract associated malignancy arising between the second-order bile ducts and the insertion of the cystic duct into the common bile duct (ICD-11 as 2C15.0)<sup>24,25</sup> (Table 2, Statement 1) and recognized that the determination of a hilar tumor's anatomic origin may occasionally be difficult, or even impossible.

#### Radiological Assessment

The use of multidetector computed tomography (MDCT), magnetic resonance imaging with cholangiography (MRI/MRCP), and 18-F fluorodeoxyglucose positron electron tomography (18-F FDG PET) in diagnosing pCCA is often dependent upon their accessibility and institutional expertise. There are no head-to-head comparisons available. The jury recognized that at least MDCT and MRI/MRCP should be performed as they serve complementary purposes, and 18-F FGD PET imaging may be employed on a case-by-case basis to detect distant metastases (sensitivity and specificity: 70%–75%).<sup>26</sup> MRI/MRCP should be performed before the endoscopic retrograde cholangiography (ERC) to minimize artifactual image degradation (Table 2, Statement 2).

#### Tumor Markers

Serum carbohydrate-antigen (CA) 19-9 and/or carcinoembryonic-antigen (CEA) levels, while being of poor diagnostic value, were identified as predictors of locally advanced and metastatic disease.<sup>27</sup> Therefore, experts and the jury agreed that CA 19-9 and CEA should be assessed at diagnosis for the evaluation of potential distant metastases (Table 2, Recommendation 3).

**TABLE 2.** Final Jury Recommendations

## Panel 1. Definition and diagnosis

1. The definition of pCCA is anatomic and has been codified by ICD11 2C18.0. It is anticipated to be included into the coming WHO classification of tumours. The determination of the origin of a mass extending from the hilum to liver parenchyma or to the gallbladder either as intrahepatic, extrahepatic cholangiocarcinoma or from the gallbladder, respectively, may occasionally be difficult, or even impossible.

*Statement: Strong [Level of Evidence: 5]*

2. It is reasonable to employ both MRI/MRCP and MDCT imaging for pCCA as they provide complementary information for staging the disease. PET scan is often used on a case-by-case basis.

*Statement: Strong [Level of Evidence: 4]*

3. Serum carbohydrate-antigen 19-9 and/or carcinoembryonic-antigen levels should be assessed at diagnosis for the evaluation of the risk of potential distant metastasis.

*Recommendation: Strong [Level of Evidence: 4]*

4. Cholangiography with brush cytology and biopsies should be performed in patients with suspected pCCA to obtain histopathological diagnosis. Cholangioscopy increases the diagnostic yield in indeterminate strictures and is endorsed by current guidelines.

*Recommendation: Strong [Level of Evidence: 3]*

5. Endoscopic ultrasound-guided biopsy of the primary lesion can be performed in patients not being considered for liver transplantation. Endoscopic ultrasound-guided fine-needle aspirates of regional lymph nodes to examine for lymph node metastases can be performed if it will alter or guide further therapeutic decision making.

*Recommendation: Weak [Level of Evidence: 3]*

6. Both conventional cytology and FISH should be used for the diagnosis of pCCA.

*Recommendation: Strong [Level of Evidence: 1]*

7. Molecular subtyping is suggested as it may provide diagnostic and predictive information, helping to discriminate pCCA from intrahepatic cholangiocarcinoma and dictating therapeutic options for the patient.

*Recommendation: Weak, [Level of Evidence: 5]*

## Panel 2. Preoperative planning and surgical resectability

8. Combining contrast-enhanced CT with contrast-enhanced MR/MRCP is recommended for determining resectability of pCCA before any biliary intervention.

*Recommendation: Strong [Level of Evidence: 3]*

9. Patients with proven distant metastatic disease (liver metastases, metastases in other organ/sites or distant lymph node metastasis), or extensive local involvement (infiltration of biliary radicals concomitant with inability to reconstruct hilar vessels inflow or bile ducts), should be considered unresectable. Inadequate Future Liver Remnant, or a medically unfit patients should not be considered for resection due to the futility of surgery.

*Recommendation: Strong [Level of Evidence: 3]*

10. None of the different staging systems can be recommended to accurately predict resectability in patients with pCCA.

*Recommendation: Strong [Level of Evidence: 4]*

11. In pCCA patients, the future liver remnant should be assessed by volumetry. Liver function should be assessed by conventional biochemical parameters, together with any functional test such as Indocyanine green clearance and <sup>99m</sup>Tc-labelled GSA or mebrofenin single-photon emission CT. Those tests should be performed after biliary drainage in case of jaundice at diagnosis.

*Recommendation: Strong [Level of Evidence: 4]*

12. The opinion of the multidisciplinary team involved in the surgical planning of pCCA patients is useful and should be considered to determine the best treatment strategy.

*Recommendation: Strong [Level of Evidence: 5]*

13. Staging laparoscopy in pCCA may be used in selected patients, such as those with clinical T3 or T4 tumors or those with a strong suspicion of distant metastases.

*Recommendation: Weak [Level of Evidence: 4]*

14. Routine staging laparoscopy is not recommended in patients with pCCA.

*Recommendation: Strong [Level of Evidence: 3]*

## Panel 3. Preoperative optimization

*Biliary drainage*

15. Biliary drainage is recommended in jaundiced patients with either cholangitis, renal or hepatic failure, severe malnutrition, disturbing symptoms such as intense pruritis, or inadequate future liver remnant before the hypertrophy technique.

*Recommendation: Strong [Level of Evidence: 2]*

16. If indicated, biliary drainage should be performed as soon as possible after diagnosis and staging in patients identified for surgical resection to allow adequate time for bilirubin reduction and liver optimization. Drainage, whatever the route, should be done according to the planned resection, with the aim to drain only the future liver remnant. Plastic stents/drains or fully covered expandable metallic stents should be placed to avoid compromising the future biliary reconstruction.

*Recommendation: Strong [Level of Evidence: 2]*

17. Superiority of endoscopic or percutaneous catheter biliary drainage in resectable biliary obstruction has not been demonstrated definitively.

*Statement: Strong [Level of Evidence: 3]*

18. The choice of endoscopic or percutaneous catheter biliary drainage should be based on tumor anatomy, patient characteristics, local expertise, and procedure availability.

*Recommendation: Strong [Level of Evidence: 4]*

19. Endoscopic biliary drainage should be preferred when allowed by tumor anatomy, especially in Bismuth type I and II lesions. Percutaneous biliary drainage should be considered in the following patient populations: (a) Complex anatomy: pCCA of Bismuth type III and IV, where multiple biliary obstructions make endoscopic access difficult, with a risk of infecting excluded sectors that are not drained. (b) Failure of endoscopic drainage: due to technical difficulties or anatomical variations. (c) Septic patients: cholangitis or sepsis requiring urgent biliary decompression when endoscopic drainage is not feasible or delayed. (d) Anatomical obstructions: cases where endoscopic access is hindered by altered gastrointestinal anatomy (eg, postsurgical alterations).

*Recommendation: Strong [Level of Evidence: 4]*

*Techniques for liver hypertrophy*

20. Assessment of the future liver remnant should be done on high-quality CT scan by calculating its volume relative to the body weight or the total estimated liver volume based on body surface area.

*Recommendation: Strong [Level of Evidence: 2]*

21. Hypertrophy techniques should be performed if the predicted future liver remnant is < 30%.

*Recommendation: Strong [Level of Evidence: 3]*

22. The cutoff for the indication of hypertrophy techniques should be increased to a future liver remnant of < 40% in case of frail patients, cholestatic livers, or status of malnutrition.

*Recommendation: Strong [Level of Evidence: 4]*

23. Portal vein embolization is recommended as the initial technique to induce hypertrophy.

*Recommendation: Strong [Level of Evidence: 3]*

24. Upfront or additional liver venous deprivation should be considered in patients needing substantial augmentation (future liver remnant < 20%–25%, altered livers and/or right extended hepatectomy).

*Recommendation: Strong [Level of Evidence: 3]*

25. ALPPS is currently not suggested as the initial procedure for future liver remnant hypertrophy, but may be an option.

*Recommendation: Weak [Level of Evidence: 5]*

*Prehabilitation and management of sepsis*

26. Prehabilitation enhances patients' resilience to surgical stress and improves postoperative outcomes. Components should include: efficient biliary drainage, nutritional optimization, physical exercise and rehabilitation, and psychological support.

*Recommendation: Strong [Level of Evidence: 5]*

27. In rare cases where patients present with sepsis, treatment should be instituted immediately with urgent biliary drainage and initiation of empiric antibiotic therapy. The interval between biliary drainage and surgery should be as short as possible after sepsis has been controlled.

*Recommendation: Strong [Level of Evidence: 4]*

28. All patients undergoing preoperative biliary drainage should receive appropriate antibiotic coverage to control existing infections or prevent them. In case of sepsis, antibiotic therapy should be adapted based on blood and bile samples during the waiting time before surgery. Antibiotic therapy should be continued several days after surgery and adapted to intraoperative samples.

*Recommendation: Strong [Level of Evidence: 4]*

#### Panel 4. Surgery

29. Major hepatectomy along with resection of segment 1 and bile duct should be considered the standard approach to aim for R0 resection.

*Recommendation: Strong [Level of Evidence: 4]*

30. Major hepatectomy is associated with a significant risk of liver failure and subsequent mortality. Left-sided hepatectomy should be considered when possible, due to the high-risk nature of right-sided hepatectomy.

*Recommendation: Strong [Level of Evidence: 4]*

31. Left trisectionectomy may be an option in tumors of Bismuth type IV, albeit technically demanding and frequently requiring hepatic arterial resection.

*Recommendation: Weak [Level of Evidence: 4]*

32. Minor liver resections, including excision of hilar bile duct with partial resection of segments 1, 4, and 5, may be an option in selected patients with compromised liver function and less advanced tumors, and can achieve comparable long-term outcomes and lower postoperative morbidity and mortality, compared with major resection.

*Recommendation: Weak, [Level of Evidence: 4]*

*Segment 1 resection*

33. In Bismuth type III-IV tumors, hemi-hepatectomy with segment 1 resection increases the chance of R0 resection, potentially improving postoperative survival.

*Statement: Strong [Level of Evidence: 4]*

TABLE 2. (continued)

34. In Bismuth type I–II tumors, the benefit of segment 1 resection remains controversial.  
Statement: Weak [Level of Evidence: 4]

35. Postoperative morbidity and mortality are comparable regardless of whether segment 1 resection is performed.  
Statement: Strong [Level of Evidence: 4]

*Lymphadenectomy*

36. Lymph node metastasis is a strong prognostic factor after resection.  
Statement: Strong [Level of Evidence: 4]

37. Regional lymph node dissection of stations #12, #8, and #13a is suggested to sample  $\geq 6$  lymph nodes.  
Recommendation: Weak [Level of Evidence: 4]

38. Extended lymphadenectomy to obtain a high number of lymph nodes is not recommended due to a lack of proven benefit.  
Recommendation: Strong, [Level of Evidence: 4]

*Vascular resections*

39. Vascular resection increases resectability in advanced tumors (cT4). Hepatectomy with vascular resection carries a higher risk of liver failure and mortality, compared with hepatectomy without vascular resection. Survival in cases with vascular resection is worse than in non-vascular-resection cases, but superior to unresectable disease.  
Statement: Strong [Level of Evidence: 3]

40. Vascular resection should be performed only when the inflow vessels to the future liver remnant adhere to the tumor. Routine no-touch technique is not recommended.  
Recommendation: Strong [Level of Evidence: 3]

41. Hepatic artery resection and reconstruction is a challenging procedure with a significant mortality rate and should be performed in experienced high-volume centers.  
Recommendation: Strong, [Level of Evidence: 4]

*Minimally invasive approach*

42. Minimally invasive surgery is a safe and feasible approach with non-inferior outcomes when performed by experienced surgeons, in experienced centers, and in selected patients, ie, those with Bismuth type I-III tumours without the need for vascular resection.  
Statement: Strong [Level of Evidence: 3]

43. Compared to laparoscopy, the robotic approach offers technical advantages in lymphadenectomy and biliary reconstruction.  
Statement: Strong [Level of Evidence: 3]

Panel 5. Morbidity and Mortality

*Morbidity and Mortality*

44. Standardized metrics for uniform morbidity assessment should include the Clavien-Dindo classification, the CCI<sup>®</sup>, and failure to rescue.  
Recommendation: Strong [Level of Evidence: 3]

45. Procedure-specific complications should include liver failure, bile leakage, wound infections, and sepsis, and should be monitored using validated definitions.  
Recommendation: Strong [Level of Evidence: 5]

46. Broader metrics, such as length of hospital stay, emergency visits, re-admissions, as well as PROMs and PREMs, should be included to assess overall morbidity and mortality comprehensively.  
Recommendation: Strong [Level of Evidence: 5]

47. Local, national, and international registries should be established to enhance data transparency, enable benchmarking, and contribute to global best practices.  
Recommendation: Strong [Level of Evidence: 5]

48. The 90-day follow-up is suggested as the minimum period for assessing cumulative morbidity. Standard follow-up is suggested to be extended to 6 months to include delayed complications, particularly in high-risk cases or complex surgeries. Differentiation between morbidity-related follow-ups from oncologic surveillance after 6 mo is suggested to avoid confounding results.  
Recommendation: Weak, [Level of Evidence: 4]

49. Prerequisites to improve outcomes include:

- Early referral to expert centers.
- A high-volume of cases to ensure experience and improved outcomes.
- Advanced surgical expertise in complex hepatobiliary procedures.
- Comprehensive preoperative optimization capabilities, including assessment and management of future liver remnant and biliary diseases.
- A multidisciplinary team approach.
- Robust postoperative care protocols and facilities for managing complications.

Statement: Strong [Level of Evidence: 3]

*Patient-centered outcomes*

50. Quality of Life assessments should be conducted at baseline, before treatment, and during early and mid-term recovery, using validated tools to capture patient-centered outcomes over time (i.e., EORTC QLQ-C30 and disease-specific modules like QLQ-BIL21).

*Recommendation: Strong [Level of Evidence: 5]*

51. Patient satisfaction with postoperative care should be evaluated regularly, focusing on key aspects such as complication management, pain control, and return to normal activities.

*Recommendation: Strong [Level of Evidence: 5]*

52. Systematic collection and analysis of PROMs and PREMs should be implemented to inform quality improvement initiatives and guide patient-centered care strategies.

*Recommendation: Strong [Level of Evidence: 5]*

#### Panel 6. Perioperative Oncological Treatments

53. Neoadjuvant therapy in patients with resectable disease is not recommended.

*Recommendation: Weak [Level of Evidence: 4]*

54. In patients with resected pCCA, a six-month course of adjuvant fluoropyrimidine therapy (capecitabine or S1) is recommended.

*Recommendation: Strong [Level of Evidence: 2]*

55. In patients with resected pCCA, adjuvant radiotherapy is not recommended.

*Recommendation: Weak [Level of Evidence: 4]*

56. The role of perioperative (neoadjuvant or adjuvant) therapy with targeted or immunotherapy remains investigational. Participation in clinical trials is suggested.

*Recommendation: Weak [Level of Evidence: 5]*

57. Molecular profiling is suggested to facilitate future targeted therapy though at present there is no proven benefit.

*Recommendation: Weak [Level of Evidence: 5]*

58. Photodynamic therapy to enable conversion to surgery in pCCA is not recommended; its use remains investigational.

*Recommendation: Strong [Level of Evidence: 5]*

#### Panel 7. Transplantation

59. Patients diagnosed with pCCA should be considered for liver transplantation based on the following characteristics: Absence of general contraindications for transplantation, presence of an unresectable tumor (for anatomic consideration or due to underlying primary sclerosing cholangitis) located above the cystic duct and 3.0 cm or less in its maximal radial diameter, with no evidence of nodal and distant metastases. Other exclusions are: attempted resection with violation of the tumor plane, positive transperitoneal biopsy of the primary tumor.

*Recommendation: Strong [Level of Evidence: 3]*

60. Patients should undergo staging including evaluation of regional nodes before enrollment for liver transplantation.

*Recommendation: Strong [Level of Evidence: 3]*

61. Patients should be treated with neoadjuvant therapy before liver transplantation.

*Recommendation: Strong, [Level of Evidence: 3]*

62. Pretransplant biliary drainage with endoscopic approach should be preferred when feasible, but percutaneous biliary drainage is acceptable and is not associated with disease recurrence.

*Recommendation: Strong [Level of Evidence: 3]*

63. Patients who undergo liver transplantation for pCCA should receive neoadjuvant chemo-radiotherapy with a total dose of 4500 cGy external beam radiotherapy with concomitant 5-FU infusion, followed by a brachytherapy boost of 1500 cGy, followed by Capecitabine maintenance for at least 3–6 months before transplantation.

*Recommendation: Strong [Level of Evidence: 2]*

64. Liver transplantation may be considered instead of resection for resectable pCCA or when there is a question of resectability preoperatively, in the setting of appropriate access to living or deceased donors.

*Recommendation: Weak [Level of Evidence: 3]*

65. In the setting of neoadjuvant chemoradiotherapy, both living donor and deceased donor liver transplantation may be considered for early-stage, unresectable perihilar cholangiocarcinoma.

*Recommendation: Weak [Level of Evidence: 3]*

#### Panel 8. Expected Outcomes

66. At present, there is no evidence that post-operative surveillance has a survival benefit, though early detection may have a benefit as more effective systemic treatment becomes available. If surveillance is chosen, a recommended strategy could be based on CT scan assessments at 3 monthly intervals in the first year and then 6 monthly to 5 years from surgery, with MRI, PET-CT and biopsy used for abnormalities or clinical suspicion of recurrence. Regular measurements of tumor markers (carcinoembryonic antigen and carbohydrate antigen 19–9) are suggested at the same time points.

*Recommendation: Weak [Level of Evidence: 5]*

67. Oncological outcome parameters should include recurrence-free survival and overall survival. In optimally treated patients with resectable tumors, those are estimated at 26 and 53 months, respectively.

*Recommendation: Strong [Level of Evidence: 1]*

68. Lymph node status, completeness of resection (R0/R1), and tumor differentiation are the most relevant predictors of pCCA recurrence and survival. These should be assessed in all pCCA-resected patients.

*Recommendation: Strong [Level of Evidence: 2]*

69. There are no defined PROMs, PREMs, and quality of life outcome expectations after surgical treatment of pCCA; however, there are quality of life questionnaires available. Development and implementation of PROMs, PREMs, and quality of life outcomes in any studies analyzing clinical outcomes after surgical treatment for pCCA are suggested.

*Recommendation: Weak [Level of Evidence: 5]*

**TABLE 2. (continued)**

70. Patients with pCCA who have relapsed after curative surgery should be considered for chemotherapy (cisplatin-gemcitabine). The addition of immune-checkpoint inhibitors should be considered unless there are contraindications to immunotherapy. No current data supports the use of immune-checkpoint inhibitors in patients with severe autoimmune diseases such as primary sclerosing cholangitis.

*Recommendation: Strong [Level of Evidence: 2]*

71. Genomic profiling is recommended when planning palliative systemic anticancer treatment.

*Recommendation: Strong [Level of Evidence: 2]*

ALPPS indicates Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy; CCI<sup>®</sup>, Comprehensive Complication Index<sup>®</sup>; cGy INDICATES Centigray; 5-FU, 5-Fluorouracil; FISH, fluorescence in situ hybridization; GSA, galactosyl human serum albumin; ICD, international classification of diseases; MDCT, multi-detector computed tomography; MRI, Magnetic Resonance Imaging; MRCP, magnetic resonance cholangiopancreatography; pCCA, perihilar cholangiocarcinoma; PET, positron emission tomography; PREMs, patient-reported experience measures; PROMs, patient-reported outcome measures; WHO, world health organization.

## Endoscopic Assessment

ERC with brushings and biopsies should be performed in patients with suspected pCCA to obtain tissue diagnosis.<sup>28,29</sup> Existing guidelines further support the selective use of supplementary cholangioscopy-guided biopsy sampling in indeterminate perihilar strictures and when the probability to obtain adequate drainage to avoid cholangitis is high<sup>30,31</sup> (Table 2, Recommendation 4). Endoscopic ultrasound (EUS) guided fine-needle aspiration (FNA) of the primary lesion is highly accurate when positive, but its negative predictive power is lower.<sup>32</sup> If transplantation is to be considered, endoscopic-guided transperitoneal FNA of the primary tumor is discouraged as it has been associated with seeding.<sup>33</sup> EUS-guided FNA has been shown to be beneficial in identifying nodal metastases, thereby guiding therapy, but still missed 34% of lymph node metastases identified surgically<sup>34,35</sup> (Table 2, Recommendation 5).

## Cytology and Pathology

Conventional cytology and transpapillary biopsy show similar sensitivity and specificity of 20% to 40% and 100%, respectively.<sup>28,30,31</sup> FISH for polysomy has a sensitivity of 60% to 70% and a specificity of ~95%.<sup>30,36,37</sup> The combined use of cytology and FISH further increases the sensitivity to 80%<sup>38</sup> and thus should be the standard approach (Table 2, Recommendation 6).

The diagnostic value of cytology can be improved using immunohistochemical and molecular techniques; for example, by the demonstration of altered p53 and Smad4 expression, or of *TP53*, *SMAD4* and *KRAS* mutations.<sup>39</sup> Although rarely present, molecular subtyping for specific targetable aberrations is encouraged, especially for assays identifying *FGFR2* fusions and specific *IDH1* gain of function mutations<sup>40</sup> (Table 2, Recommendation 7).

## Panel 2. Preoperative Planning and Surgical Resectability

### Imaging to Assess Resectability

Contrast-enhanced MDCT and MRI/MRCP are complementary in assessing surgical resectability and thus should be combined<sup>41</sup> (Table 2, Recommendation 8). High-quality cross-sectional imaging should be done before any biliary intervention, as it minimizes artifactual image degradation and reduces the risk of misinterpreting post-intervention inflammatory changes.<sup>42</sup> The strengths of contrast-enhanced MDCT lie in its high spatial resolution and low motion artifacts, therefore allowing for precise assessment of horizontal tumor spread and vascular involvement. MRI on the other hand improves sensitivity in evaluating tumor extent along the bile duct and invasion of the liver,<sup>43</sup> and increases accuracy for detecting lymph node metastases.<sup>44</sup> The added value of F-18 FDG PET to assess anatomical resectability is limited.<sup>45,46</sup>

### Criteria of Unresectability

Experts agreed that infiltration of biliary radicals combined with the inability to reconstruct hilar vessel inflow and/or bile ducts, as well as proven metastatic disease to the liver, other organs, or distant lymph nodes should generally preclude surgery. Some data suggest that CA 19-9 levels  $\geq 1000$  U/L translate into advanced disease, which may not benefit from surgery.<sup>47</sup> Underlying liver disease due to primary sclerosing cholangitis (PSC) is also an important

consideration in determining unresectability. In addition, surgical planning relies on both the volume and function of the future liver remnant (FLR).<sup>8,27,48</sup> In contrast to age alone,<sup>49</sup> poor performance status represents a proven independent prognostic indicator.<sup>6,7,48,49</sup> In synthesis, the jury considered anatomical, biological, and conditional criteria as part of the definition of unresectability (Table 2, Recommendation 9). These proposed expert opinion-based resectability criteria (Fig. 2, Supplemental Table 5, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>) require further validation.

### Classifications to Assess Resectability

None of the available classifications were developed to primarily determine surgical resectability and their evaluation for this purpose is based on retrospective analyses only. Studies evaluating the Bismuth-Corlette<sup>50,51</sup> and the Memorial Sloan-Kettering Cancer Center staging system<sup>50–52</sup> found highly variable resectability rates across tumor stages. Other classifications either depend on postoperative histopathological findings, not available in the preoperative setting<sup>53</sup>, or have never been assessed for their ability to predict surgical resectability.<sup>11,12</sup> Therefore, none of the available staging systems can be recommended to accurately predict resectability (Table 2, Recommendation 10).

### Assessment of Liver Parenchyma

Most studies evaluating preoperative volumetric and functional assessment are based on non-pCCA patients. Few retrospective studies confirmed that FLR volume-to-body weight ratio,<sup>54</sup> indocyanine green retention rate at 15 minutes (ICG R15),<sup>55</sup> 99mTc-labelled GSA<sup>56,57</sup> and 99mTc-labelled mebrofenin SPECT<sup>58</sup> may predict the risk of post-hepatectomy liver failure (PHLF) also in pCCA patients. Experts and the jury unanimously recommended that liver volume should be assessed by volumetry (Table 2, Recommendation 11). In line with recent consensus for preoperative functional assessment,<sup>59</sup> this should be complemented with clinical assessment, blood-based scores, ICG clearance or LiMAX, and liver scintigraphy according to local expertise and availability (Table 2, Recommendation 11). One key limitation in the setting of pCCA is the elevated bilirubin levels hampering interpretation of ICG, liver scintigraphy and single-photon emission CT (SPECT) due to competitive bilirubin uptake.

### Multidisciplinary Management

Several noncomparative studies and surveys highlighted the favorable impact of centralization and multidisciplinary evaluation on perioperative outcomes.<sup>9,60,61</sup> Among 61 European centers, multidisciplinary case discussion was routinely performed in 92% and is currently considered part of good clinical practice.<sup>9,60</sup> The jury strongly endorsed that synergy of hepatologists, endoscopists, radiologists, radiotherapists, oncologists, and surgeons is mandatory to discuss the appropriate treatment strategy (Table 2, Recommendations 12).

### Staging Laparoscopy

Staging laparoscopy can help detect radiologically occult peritoneal dissemination or minute liver metastasis.<sup>62</sup> Reported accuracy ranges from 32% to 66%, though these rates have decreased with advancements in imaging technology.<sup>63,64</sup> In addition, laparoscopy appears to be a poor modality for determining the local

advancement and anatomical resectability.<sup>65</sup> Consequently, experts and the jury would consider staging laparoscopy in selected patients, such as those with T3 or T4 tumors or those with strong suspicion of distant metastases, but advise against its routine use (Table 2, Recommendation 13–14).

### Panel 3. Preoperative Optimization

Preoperative optimization plays a fundamental role in improving short-term and long-term outcomes in pCCA treatment with curative intent and includes preoperative biliary drainage, the evaluation of the FLR and its augmentation techniques, management of sepsis, and prehabilitation.

#### Biliary Drainage

Biliary drainage improves jaundice, pruritus, coagulopathy, and renal failure, while possibly optimizing liver function and hypertrophy before surgery.<sup>66,67</sup> Recent meta-analyses, however, demonstrated contradictory results with higher morbidity but similar mortality for patients receiving biliary drainage compared with those without.<sup>68–70</sup> Importantly, these results were largely dependent on bilirubin levels, FLR volume, and type of hepatectomy.<sup>69,71</sup> Based on this, experts and the jury agreed that biliary decompression should be performed in jaundiced patients with either small FLR requiring hypertrophy techniques, cholangitis, renal or hepatic failure, severe malnutrition, or disturbing symptoms such as intense pruritus (Table 2, Recommendation 15).

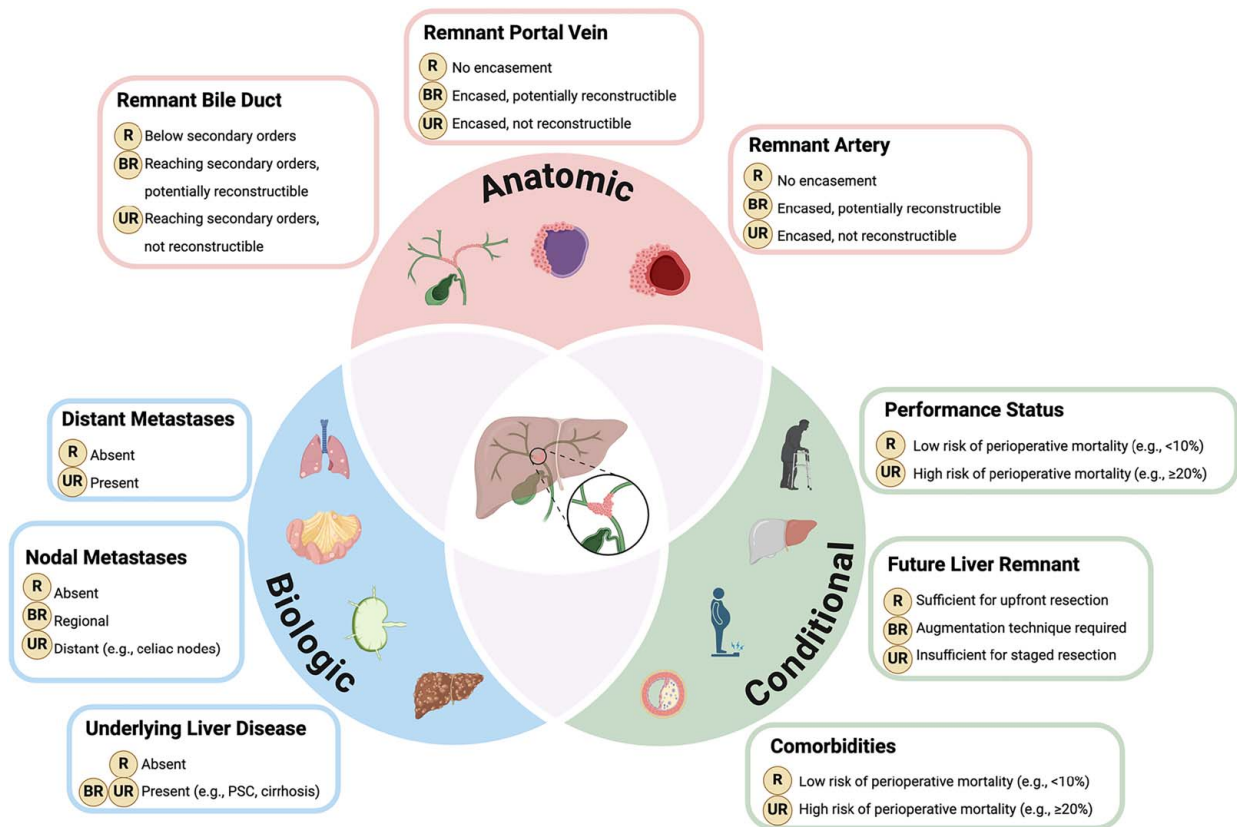
Drainage should be performed as soon as possible after diagnosis in patients identified for surgical resection to allow adequate time for bilirubin reduction and liver optimization. The optimal threshold of preoperative bilirubin after drainage is still a matter of debate.<sup>72</sup> Drainage—whatever the route—should be done in collaboration with the surgeon according to the planned resection, with the aim to exclusively drain the FLR<sup>73</sup> (Table 2, Recommendation 16).

#### Route for Biliary Drainage

The superiority of one drainage route over the other has not been demonstrated conclusively (Table 2, Statement 17). Both RCTs<sup>74,75</sup> comparing endoscopic biliary drainage (EBD) to percutaneous biliary drainage (PBD) were prematurely closed. International guidelines recommend EBD as the primary modality<sup>76</sup> or both approaches equally<sup>77</sup> based on larger scale retrospective evidence,<sup>78,79</sup> but PBD remains the preferred approach in the majority of centers.<sup>9</sup> Consequently, the choice should be made on an individual basis, taking tumor stage and anatomy, patient characteristics, local expertise, and procedure availability into account (Table 2, Recommendations 18 and 62). While recognizing EBD as the preferred approach when allowed by tumor anatomy, the consensus outlined scenarios defining evidence-based indications for primary PBD. These include complex anatomical cases reaching the technical limitations of EBD, failed EBD, and altered gastrointestinal anatomy precluding endoscopic passage (eg, postsurgical reconstruction) (Table 2, Recommendation 19).

#### Assessment of FLR Volume

Most studies evaluating different approaches to assess FLR volume are not specific to pCCA. In general, FLR volume estimated using a high-quality CT scan and standardized to total estimated liver volume (TELTV) or body weight should be preferred.<sup>54,59</sup> Total liver volume based on actual measurement appears particularly



**FIGURE 2.** Comprehensive evaluation approach to determine surgical resectability. Abbreviations: R (Resectable); BR (Borderline Resectable); UR (Unresectable); PSC (Primary Sclerosing Cholangitis)

inaccurate in patients who undergo unilateral biliary drainage and/or potential atrophy due to biliary obstruction.<sup>80</sup> Formulae based on body surface area (BSA) and specifically the Vauthey formula<sup>81</sup> (TELV (mL) = 1267.28 × BSA (m<sup>2</sup>)) appear most accurate<sup>82</sup> (Table 2, Recommendation 20).

While a FLR of >30% proved sufficient in healthy liver parenchyma,<sup>83,84</sup> a threshold at 30% comes with an increased risk in the presence of diseased livers, such as in cirrhosis, chemotherapy-associated liver injury, or persistent cholestasis.<sup>85–88</sup> Preoperative cholangitis and low albumin levels were additionally associated with an increased risk of PHLF in multicenter retrospective studies.<sup>89,90</sup> Therefore, the jury endorsed the FLR cutoff of ≥30% for pCCA patients with healthy liver parenchyma (Table 2, Recommendation 21) and suggested that this cutoff be increased to at least 40% in frail or comorbid patients, or those with cholangitis, cholestatic livers, or malnutrition (Table 2, Recommendation 22).

**Techniques for Liver Hypertrophy**

Proven safe and effective, with an average FLR hypertrophy of 8–27%, an overall complication rate of 3%, and zero mortality,<sup>91,92</sup> portal vein embolization (PVE) should be the first choice to induce FLR hypertrophy in pCCA patients<sup>92,93</sup> (Table 2, Recommendation 23). PVE should be performed without delay once decreasing bilirubin levels indicate effective drainage to reduce the risk of infectious complications.<sup>94</sup> Known drawbacks of PVE include failure to induce sufficient FLR growth, disease progression,<sup>91,92,95</sup> and the risk of glue reflux to the FLR in

segment 4 embolization for extended right hepatectomy (H45678).<sup>96</sup>

Upfront or additional liver venous deprivation (LVD) may be an alternative in patients at risk of PVE failure<sup>97</sup> because of its increased liver growth and putative reduced PHLF compared with PVE.<sup>98–102</sup> Limited data in pCCA patients<sup>103</sup> showed better functional results and similar morbidity for LVD compared with PVE. The jury acknowledged that at this point LVD should be reserved for patients with expected impaired regenerative capacity or the need for substantial augmentation, that is, in patients with a FLR of <20% to 25%, altered liver parenchyma and/or those requiring right extended hepatectomy (Table 2, Recommendation 24).

Despite significant improvements for other indications, Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)<sup>104</sup> in pCCA patients remains associated with increased morbidity and mortality,<sup>105</sup> although prospective head-to-head comparisons and RCTs comparing ALPPS to other techniques are lacking. Only one recent multicenter study (8 centers, n=39) reported acceptable short-term and long-term results in selected pCCA patients treated in expert centers.<sup>106</sup> Therefore, the jury limited the role of ALPPS in pCCA to that of a salvage procedure if other hypertrophy techniques fail, while the primary use of ALPPS is not suggested (Table 2, Recommendation 25).

**Prehabilitation and Sepsis Management**

The benefit of prehabilitation has been validated in major abdominal surgery,<sup>107</sup> but data on its specific role in

pCCA patients remains limited. A prehabilitation program was found to improve physical performance, lower complication rates and shorten postoperative stay for major liver surgery in general.<sup>108</sup> Preoperative sarcopenia/sarcopenic obesity is a risk factor for worse postoperative outcomes in retrospective studies.<sup>109–111</sup> The jury recognized this collective evidence to generally be applicable to pCCA patients and highlighted key preoperative interventions: nutritional optimization, physical exercise, and psychological support (Table 2, Recommendation 26).

For patients presenting with sepsis, the jury—in line with international guidelines on surviving sepsis<sup>112</sup>—supported the practice of combined focus control and systemic antibiotic therapy along with supportive measures (Table 2, Recommendation 27). Effective biliary drainage with concomitant empiric antibiotic therapy should be established urgently (Table 2, Recommendation 27), and then adjusted based on blood and bile samples as soon as possible (Table 2, Recommendation 28).

#### Panel 4. Surgery

Major hepatectomy along with resection of segment 1 and bile duct<sup>113</sup> is currently considered the standardized approach to achieve R0 resection<sup>42,114</sup> (Table 2, Recommendation 29). The body of evidence on surgical resection of pCCA, however, is of a retrospective nature with large multicenter<sup>115,116</sup> and one benchmark study,<sup>2</sup> as well as two meta-analyses<sup>117,118</sup> representing the highest level of evidence. While the side of liver resection is predominantly predetermined by anatomical reasons,<sup>116</sup> right-sided major hepatectomy, though oncologically equivalent, is generally associated with increased procedure-related morbidity, liver failure (PHFL), and mortality compared with left-sided resections.<sup>2,116,118,119</sup> Consequently, experts and the jury concluded that left-sided hemi-hepatectomy (H1234-B<sup>120</sup>) should be chosen, if possible (Table 2, Recommendation 30). Despite its high technical demand and more frequent arterial resection/reconstruction, left trisectionectomy (H123458-B<sup>120</sup>) appears oncologically superior to left hemi-hepatectomy<sup>121</sup> (H1234-B<sup>120</sup>) and may be better than right trisectionectomy<sup>122</sup> (H145678-B<sup>120</sup>) in terms of PHLF and OS in advanced and Bismuth-Corlette type 4 tumors (Table 2, Recommendation 31).

The putative benefits of minor liver resections (ie, excision of liver (sub-)segments surrounding the liver hilum (segments 1, 4b, 5) with resection of the extrahepatic bile duct) for patients with limited liver function must be weighed against the oncological need for radical resection, which remains the determining factor for long-term outcome. Evidence of the efficacy of minor liver resection remains limited to small single-center retrospective studies with profound selection bias,<sup>123–127</sup> generally demonstrating lower or comparable morbidity to major hepatectomy with no differences in long-term survival. Therefore, minor liver resections may be an option only in very selective patients with compromised liver function and less advanced tumor load (Table 2, Recommendation 32).

#### Segment 1 Resection

Four meta-analyses and systematic reviews of retrospective studies<sup>117,128–130</sup> demonstrated higher R0 resection rates, with similar morbidity/mortality, and better OS for segment 1 resection in combination with left or right hemihepatectomy (Table 2, Statement 35). Based on this evidence, experts and the jury agreed that total segment 1

resection combined with left (H1234-B<sup>120</sup>) or right (H15678-B<sup>120</sup>) hemihepatectomy for patients with Bismuth-Corlette Type 3 to 4 tumors offers a higher chance for R0 resection and improved survival (Table 2, Statement 33). The benefit of total segment 1 resection for patients with Bismuth-Corlette type 1 to 2 tumors remains, however, controversial<sup>128,129</sup> (Table 2, Statement 34).

#### Lymphadenectomy

The prevalence of positive resected lymph nodes (LN) in pCCA ranges from 16% to 60%, with LN involvement being a strong prognostic factor for long-term patient survival<sup>131–135</sup> (Table 2, Statement 36). Positive LN are predominantly located in the hepato-duodenal ligament, that is, station #12 (25%), the common hepatic artery, that is, station #8 (14%), and the area posterior to the head of the pancreas, that is, station #13A (11%).<sup>136</sup> The jury, therefore, recommended to perform a regional LN dissection of these stations to provide adequate staging (Table 2, Recommendation 37). Resecting at least 5 to 7 LN is usually recommended.<sup>131–133</sup> There is, however, no benefit of extended lymphadenectomy (ie, to the celiac axis, superior mesenteric artery, periaortic LN)<sup>137–139</sup> (Table 2, Recommendation 38).

#### Vascular Resections

Vascular resection, particularly hepatic artery (HA) resection, is generally associated with increased risk of short-term morbidity and mortality compared with hepatectomy without vascular resection,<sup>140–142</sup> yet increases resectability in advanced tumors and thus improves long-term survival compared with no resection at all<sup>141,143,144</sup> (Table 2, Statement 39). Impaired safety of portal vein (PV) resection is primarily derived from early series, with more recent studies showing comparable results, indicating that PV resection may be reasonably safe when performed with sufficient experience.<sup>145</sup> HA resection remains a challenging procedure with a significant mortality rate<sup>145,146</sup> and should be performed only in experienced high-volume centers (Table 2, Recommendation 41). Exceptionally favorable results for vascular resection are so far not reproducible outside the Nagoya setting.<sup>143</sup>

While routine PV resection as in the «no touch» technique for right-sided hepatectomy (ie, en-bloc resection without isolation of the vascular pedicle at the hilum)<sup>147,148</sup> was associated with increased morbidity and mortality in some studies,<sup>2,149</sup> others found comparable results to selective vascular resection.<sup>150–153</sup> There is currently no robust evidence demonstrating its postulated oncologic superiority.<sup>2,149</sup> Based on this ambiguity, the jury concluded that at this point, vascular resection cannot be recommended on a routine basis, but may be performed selectively (Table 2, Recommendation 40).

#### Minimally Invasive Approach

Systematic reviews and meta-analyses<sup>154–156</sup> comparing pooled laparoscopic and robotic cohorts to the open approach deemed minimally invasive surgery (MIS) feasible in selected patients when performed by experienced surgeons and centers (Table 2, Statement 42). Laparoscopy is generally associated with similar long-term survival,<sup>157–159</sup> shorter length of stay,<sup>159</sup> and lower transfusion rates<sup>160</sup> compared with open surgery. To date, no head-to-head comparison between laparoscopy and the robot is available for pCCA. The highest level of evidence for the robotic

approach<sup>161</sup> documents its safety, feasibility, and oncologic adequacy, but long-term results are lacking. In line with recent international consensus,<sup>18</sup> the jury acknowledged that while more evidence comparing the robotic to the open approach is needed, it may offer inherent technical advantages over laparoscopy in lymphadenectomy and biliary reconstruction (Table 2, Statement 43).

### Panel 5. Morbidity and Mortality

The critical appraisal of treatment success based on well-defined outcome metrics is imperative. Prerequisites for surgeons and institutions to ensure patient safety and achieve optimal oncological outcome are paramount. Finally, a focus is needed on the best reporting method from the patient perspective.

### Morbidity and Mortality

Experts and jury members unanimously supported standardized reporting of surgical morbidity using validated metrics endorsed by recent recommendations for assessing outcomes of a variety of surgical interventions.<sup>3,17</sup> This included the Clavien-Dindo Classification (CDC),<sup>162–164</sup> the CCI®,<sup>1,164–166</sup> and Failure to Rescue (FTR)<sup>167–170</sup> (Table 2, Recommendation 44). These should be complemented with established procedure-specific complications such as PHLF, bile leakage,<sup>171–175</sup> infectious complications,<sup>176</sup> and sepsis,<sup>177</sup> as well as broader metrics including length of hospital stay, emergency visits, re-admissions, and patient-centered outcomes (Table 2, Recommendations 45 and 46). Both in-hospital and 90-day morbidity and mortality should be consistently recorded. Importantly, establishing regularly audited local, national, and international registries to enhance data transparency and ensure quality of reporting is an unmet need (Table 2, Recommendation 47).

### Follow-up Period

Experts and the jury recognized the standard 90-day reporting period in major liver surgery,<sup>178</sup> including for pCCA.<sup>2,3</sup> To address the risk of missing late complications, such as biliary strictures and cholangitis,<sup>166,179</sup> extending the follow-up to at least 6 months is suggested, particularly in high-risk cases or complex surgeries. Beyond the 6-month cutoff, clear differentiation between surgical morbidity metrics and oncologic progression<sup>180</sup> is required (Table 2, Recommendation 48). Capturing delayed biliary complications is more relevant after LT, in which follow-up should cover at least the first year after surgery, as evidenced in recent benchmark studies.<sup>5,181,182</sup>

### Prerequisites for Excellence

The consensus underlines the critical role of expertise as a pre-requisite for providing adequate quality of care in every step of patient management.<sup>2,3,183–187</sup> The jury recognized multiple factors impacting on postoperative outcomes (Table 2, Statement 49). High-volume expert centers treating complex (nonbenchmark) cases have reduced postoperative mortality compared with centers limiting their practice to low-risk patients.<sup>2</sup> The availability of experienced multidisciplinary teams and standardized postoperative care protocols improves complication prevention and management with reduced morbidity and mortality.<sup>3,183,187</sup> Surgeons must be skilled in complex hepatectomies requiring biliary reconstructions and vascular resections.<sup>2,184–186</sup> Importantly, experts and the jury

unanimously recognized the importance of early referral to expert centers.

### Patient Perspective

To date, reporting of patient-centered outcomes in pCCA is grossly lacking and can only be derived from studies reporting on general hepatobiliary malignancy<sup>188–190</sup> or major liver resection<sup>191–193</sup> populations. Therefore, routinely capturing the patient's perspective was identified as an essential need in future studies.<sup>194</sup> This should comprise standardized reporting of Quality of Life (QoL), patient satisfaction, and patient reported metrics (PROM, PREM) at standardized timepoints, that is, at baseline, before treatment, and during short-term (3 mo) and longer-term (eg, 6 and 12 mo) follow-up (Table 2, Recommendation 51). While acknowledging the potential need for further disease-specific adjustment in the future, the consensus agrees that validated QoL scores, PROMs, and PREMs (eg, EORTC QLQ-C30,<sup>195</sup> QLQ-BIL21,<sup>190</sup> FACIT,<sup>196</sup> PROMIS<sup>197</sup>) best represent the patient's perspective and should be tested in the setting of pCCA (Table 2, Recommendations 50, 52, 69).

### Panel 6. Perioperative Oncological Treatment

#### Neoadjuvant Chemotherapy

Evidence for neoadjuvant chemotherapy (NAC) is primarily derived from retrospective<sup>198,199</sup> and prospective single-center<sup>200,201</sup> cohort studies focusing on anatomically defined borderline resectable and locally advanced disease. NAC regimens generally failed to improve disease-free survival (DFS) or OS but showed possible tumor downsizing with improved surgical eligibility<sup>198</sup> and even R0 resection rates.<sup>202–204</sup> Prospective studies additionally found high disease control rates,<sup>200</sup> higher resection rates even in locally advanced scenarios,<sup>201</sup> and prolonged OS in resected patients.<sup>200</sup> These observations, however, need to be interpreted in the absence of uniform criteria defining the local extent of the disease and its resectability. The jury concluded that while NAC shows promise as a strategy to enhance resectability, prospective studies to establish its efficacy are necessary, particularly in borderline resectable and locally advanced disease (Table 2, Recommendation 53).

#### Adjuvant Therapy

RCTs demonstrating benefits of adjuvant chemotherapy in pooled biliary tract cancer (BTC) populations failed to identify improvements in recurrence-free survival (RFS)<sup>205–207</sup> or OS<sup>205–208</sup> in pCCA patients, though were not adequately powered for this subgroup. A systematic review and meta-analysis (1 prospective and 18 retrospective studies)<sup>209</sup> and two propensity-score matched registry studies<sup>210,211</sup> found superior OS in the pCCA subgroup with adjuvant regimens. The jury concluded that for patients with resected pCCA, a 6-month course of adjuvant fluoropyrimidine therapy (capecitabine or S-1) is justified, acknowledging the need for more robust evidence in this subgroup of biliary tumors with appropriate stratification of risk features, such as nodal status and resection margin (Table 2, Recommendation 54).

#### Radiotherapy

The efficacy of adjuvant radiotherapy remains controversial, with studies showing either no survival benefit,<sup>212–214</sup> a benefit with radiotherapy alone,<sup>215,216</sup> or

with combined chemo-radiotherapy.<sup>211,217,218</sup> Key limitations lie in the variability across studies in patient selection, risk features, and treatment regimens. Benefits were particularly present in patients with R1<sup>215–218</sup> and N1 disease.<sup>212,213,217,218</sup> The relative contribution of radiotherapy in multimodal adjuvant regimens remains, however, unproven,<sup>211,213,217,218</sup> while the jury emphasized the need for clinical trials to establish the contribution of radiotherapy in the setting of multimodal therapies (Table 2, Recommendation 55).

### Targeted and Immunotherapy

The effectiveness of neoadjuvant or adjuvant targeted therapy and immunotherapy remains investigational (Table 2, Recommendation 56). Only one single-center retrospective study<sup>219</sup> on adjuvant chemo-immunotherapy in patients at higher risk of disease relapse (ie, N+, MVI+, PNI+, R1, or poor differentiation) showed superior median OS compared with adjuvant chemotherapy and surgery alone. The results of ongoing prospective studies, including ARTEMIDE-Biliary01 (NCT06109779), BTC-CaLenT (NCT05254847), and MRD-GI (NCT05482516), evaluating immunotherapy in biliary tumors, are awaited. The jury emphasized molecular profiling to facilitate future targeted therapy, although there is no proven benefit from such early assessment because of tumor heterogeneity along evolution (Table 2, Recommendation 57).

### Locoregional Treatments

Data on locoregional treatments in pCCA remains scarce with no studies investigating hepatic arterial infusion chemotherapy or irreversible electroporation in a curative setting. Evidence for the use of photodynamic therapy is limited to a systematic review,<sup>204</sup> including data from three studies (two prospective studies<sup>220,221</sup> and a case report,<sup>204</sup> total n = 16). Based on these preliminary results, the use of photodynamic therapy in pCCA remains investigational (Table 2, Recommendation 58). No recommendation can be made on other locoregional treatments.

## Panel 7. Transplantation

The role of LT in treating selective patients with pCCA remains the hottest topic since the inaugural Mayo Clinic protocol.<sup>222–224</sup> Previous anecdotal reports have only demonstrated poor and unacceptable outcomes.<sup>225,226</sup> The current debate primarily evolved around adequate patient selection, possibly also including those with resectable disease, and identifying the optimal pretransplant treatment protocols, and the role of living donation.

### Patient Selection

Most studies follow the empirically derived selection criteria rooted in the Mayo protocols,<sup>222–224</sup> which combine neoadjuvant chemo-radiation along with rigorous inclusion and exclusion criteria (Supplemental Table 6, Supplemental Digital Content 1, <http://links.lww.com/SLA/F498>). This Mayo protocol has been convincingly validated in a large multicenter cohort (n = 214).<sup>227</sup> The jury acknowledged critical components of patient selection to include patient history, tumor macro-morphologic characteristics, absence of intrahepatic or extrahepatic metastases, and completion of neoadjuvant therapy, in both unresectable tumors and those associated with PSC (Table 2, Recommendation 59). Meticulous proof of negative regional lymph nodes requires

proper staging and is essential before enrollment for LT (Table 2, Recommendation 60).

### Resectable Disease

The superiority of LT over resection in patients with upfront resectable disease remains controversial, although clearly established in a recent benchmark study involving 17 high-volume centers.<sup>5</sup> While R0 resection rates are undoubtedly superior in LT, the available data on OS remains imprecise.<sup>5,228–230</sup> After adjustment for negative margins and lymph node involvement, both clear advantages in the transplant group<sup>228</sup> and no differences in survival<sup>230</sup> have been reported. The TRANSPHIL RCT (NCT02232932) comparing resection versus LT failed in recruitment.<sup>231</sup> Based on this evidence, the jury acknowledged the potential benefit of LT limited to node-negative patients independent of resectability. But such strategy must be balanced against limited access to liver grafts with a potential benefit for living donation (Table 2, Recommendation 64).

### Living Donation

The survival benefit from living donor liver transplantation (LDLT) compared with deceased donor liver transplantation (DDLT) in end-stage liver disease is well proven.<sup>232–234</sup> In transplant oncology, however, waiting time bridged with neoadjuvant therapy often serves as a “natural history” selection tool,<sup>235</sup> while also maximizing radiation-induced tumor regression, and minimizing inflammation and fibrosis. Recent recommendations<sup>236,237</sup> deemed LDLT appropriate for oncologic indications when the anticipated post-LT survival benefit exceeds 50% at 5 years, which is de facto established in pCCA (5-yr OS: 53%).<sup>227</sup> The jury, while acknowledging technical challenges related to vasculature (ie, potential need of arterial and venous jump grafts) in LDLT,<sup>238,239</sup> concluded that both LDLT and DDLT provide effective treatment and may be considered (Table 2, Recommendation 65).

### Neoadjuvant Protocol

Waitlist and post-LT outcomes for patients with pCCA who received neoadjuvant therapy have consistently been reported to be superior in terms of OS and tumor recurrence to those omitting neoadjuvant therapy.<sup>4,5,240</sup> A recent benchmark study similarly reported inferior results in a small subgroup of 27 patients not receiving neoadjuvant therapy before LT.<sup>5</sup> Consequently, the jury recommended that patients who undergo LT for pCCA must receive a neoadjuvant regimen (Table 2, Recommendations 61 and 63). Most available series used the Mayo protocol based on external beam radiotherapy (total dose: 4500 cGy) with concomitant 5-FU infusion as radiosensitizer, followed by brachytherapy boost (1500 cGy) and oral capecitabine for at least 3 to 6 months before LT.<sup>5,235,241</sup> Several centers have omitted the brachytherapy and instead used additional external beam radiotherapy or stereotactic body radiotherapy.<sup>5</sup>

## Panel 8. Expected Outcomes

### Surveillance

Current recommendations on surveillance depend on expert opinion and protocols published by surgical series, with no evidence so far indicating a survival benefit associated with more aggressive surveillance. Experts and the jury, however, recognized the importance of early

detection of recurrent disease, as more treatment options in the form of targeted and immunotherapies are emerging,<sup>242,243</sup> and chemotherapy is effective in the palliative setting<sup>244</sup> (Table 2, Recommendation 66). Experts have favored a strict surveillance protocol based on regular CT scans (3 monthly intervals in the first year, then every 6 months thereafter) along with the measurement of tumor markers (CEA and CA 19-9), over the course of five years, as it best reflects the current standard of care. The use of MRI, PET-CT, and biopsy should be restricted to suspicious findings.

### Oncological Outcome

The main metric to assess long-term oncological outcome remains OS, which is estimated at a median of 53 months based on evidence from phase III clinical trials (pooled BTC, R0: 62%, N0: 52%)<sup>208,245,246</sup> (Table 2, Recommendation 67). The jury recognized RFS, which is currently estimated at a median of 26 months,<sup>208,245,246</sup> as a potential valid surrogate for the design of future clinical trials, but also highlighted its limitations, such as not considering the efficacy of treatments for recurrence and variability in the criteria used to identify and define recurrence. On the other hand, using RFS as an endpoint may help facilitate trial designs and deliver results in a timely manner.<sup>247</sup> In addition, novel targeted therapies introduce marked heterogeneity of response across palliative regimens,<sup>242,243</sup> which cannot be captured by a single OS endpoint.

### Prognostic Factors

The jury recognized that a comprehensive understanding of perioperative prognostic factors is crucial to optimize outcomes and identify effective management strategies (Table 2, Recommendation 68). Large retrospective observational studies identified lymph node involvement,<sup>8,132,133,210,248–251</sup> R1 resection,<sup>132,248,250</sup> and poor tumor differentiation<sup>8,248,249,252</sup> as independent oncologic factors negatively affecting OS and RFS. In addition, American Society of Anesthesiology (ASA) score  $\geq 3$ , bilirubin of  $\geq 50$  mmol/L at diagnosis, CA 19-9  $\geq 100$  U/mL, preoperative cholangitis, portal vein involvement, tumor diameter  $\geq 3$  cm, and left-sided resection, were identified as independent predictors of futility for upfront surgery in 2271 patients from 27 referral centers,<sup>253</sup> which should be considered in the process of decision making.

### Recurrent Disease

Treatment of recurrence relies on evidence from broader studies in biliary tumors, though specific data on pCCA are limited. Randomized and large retrospective multicenter data indicate benefits for cisplatin-gemcitabine,<sup>244</sup> and durvalumab+cisplatin-gemcitabine regimens<sup>243,254</sup> for the entire biliary tumor cohort, but no conclusive results for pCCA patients. Therefore, the consensus agreed that combined cisplatin-gemcitabine treatment should be the mainstay of recurrent pCCA, with additional immune-checkpoint inhibitors (Table 2, Recommendation 70). Of note, immunotherapy remains untested in pCCA associated with PSC due to trial exclusions. Targetable molecular alterations (ie, KRASG12c, HER2 amplifications, MDMD2 amplifications, BRAF mutations) may be present in pCCA,<sup>255,256</sup> justifying genomic profiling when planning palliative systemic treatment (Table 2, Recommendation 71).

### FUTURE RESEARCH PRIORITIES

The level of evidence for many aspects of pCCA remains poor, which underscores the need for various research activities. Surgical series are typically restricted to a single or few institutions, limiting the generalizability of findings, and most high-level studies have failed during the recruitment phase.<sup>74,231,257</sup> In addition, RCTs<sup>205,208,246</sup> on pooled biliary tumor populations are underpowered for pCCA. Also, novel breakthroughs in cancer therapy, such as targeted and immunotherapies or robotically assisted liver resection, are still scarce and not ready for wide use. Collaborative directed efforts in designing and executing clinically meaningful studies are needed.

Therefore, a mission of this consensus conference was to prioritize areas in need of further investigation and research. The jury emphasized the necessity of overcoming difficulties in conducting prospective comparative trials through the implementation of large-scale national and international registries collecting longitudinal data, including all treatment options and across all tumor stages. To ensure data quality, regular external auditing is indispensable. Such databases are particularly important for assessing rarely performed and technically challenging surgical procedures (ie, vascular resections, minimally invasive surgery, liver transplantation), evaluating long-term oncological results, and supporting the generalizability of trial results.<sup>258</sup> Prospective databases must capture standardized outcome parameters of clinical relevance and adhere to predetermined follow-up periods. The jury acknowledged previous efforts of defining such metrics,<sup>1,3,17,162–168,171–175</sup> and specifically encouraged prioritizing the inclusion of patient-centered outcomes<sup>190,195–197</sup> and adapting those to pCCA through real-world, multi-stakeholder analyses. Then, the jury adopted a set of recommendations deemed critical for improving quality of care, based on the knowledge gaps identified by each expert panel across the entire disease continuum (Table 3).

### DISCUSSION

The Consensus4pCCA initiative is the first jury-based consensus conference aimed at establishing comprehensive, evidence-based guidance on the multidisciplinary management of pCCA. This international conference sought to address inconsistencies in definition, diagnosis, and treatment strategies across institutions worldwide, with the primary goal of ensuring optimal care and the best achievable oncological outcome. Adhering to the validated Zurich-Danish model, the initiative evaluated most aspects of the disease, including liver transplantation and defined relevant outcomes and metrics to facilitate optimal comparison of treatment strategies. Another key aspect was an emphasis on areas requiring future investigation.

pCCA is one of the most challenging tumors still associated with poor outcome, in part due to the lack of a consistent approach to most aspects of the disease. The low frequency of the condition, as well as the paucity of high-level data, has further prevented the development of unanimously accepted guidelines. On top of those shortcomings, the recent advent of liver transplantation in curing some of these patients may have added confusion to the therapeutic options.

The systematic and comprehensive review, an essential part of this consensus effort covered by a group of young academic surgeons, has revealed substantial heterogeneity in the level of evidence in most aspects of pCCA. Consequently, several consensus discussions were primarily guided by

**TABLE 3.** Areas in Need of Future Investigation

## Definition and diagnosis

- Strategies to improve early disease detection, with a special focus on the role of radiomics and artificial intelligence
- Identification of disease-defining epigenetic alterations and genetic aberrations in tissue and bile
- Evaluation of the utility of liquid biopsy for therapeutic decision making in the absence of tissue samples

## Preoperative planning and surgical resectability

- Strategies to improve diagnostic precision for nodal metastases through radiomics and artificial intelligence applied to cross-sectional imaging
- Techniques for improved identification of perineural invasion
- Strategies for precise preoperative assessment of the extent of the disease, including peroral cholangioscopy-guided forceps mapping
- Approaches to accurately map skip lesions
- Validation of criteria defining resectable, borderline-resectable, and unresectable disease
- Development of novel staging systems with the primary goal of accurately predicting resectability
- Novel tools to assess liver parenchyma background, including nuclear tracers or functional MRI
- Development of preoperative oncological risk scores to optimize patient selection
- Identification and assessment of predictors of disease recurrence and overall survival in prospective studies

## Preoperative optimization

- Strategies for preoperative downstaging
- Comparison of preoperative endoscopic and percutaneous biliary drainage in resectable pCCA in randomized controlled studies
- Identification of the optimal time interval between biliary drainage and portal vein embolization
- Identification of the optimal antibiotic protocol in patients with biliary drainage
- Head-to-head comparison of portal vein embolization and liver venous deprivation in patients with a future liver remnant of <25%
- Strategies for improved perioperative patient management, including nutritional protocols and enhanced recovery after surgery protocols

## Surgery

- Validation of the concept of surgical success
- Comparison of minimally invasive to open surgery, including Bismuth type IV tumors, in randomized controlled studies
- Comparison of the laparoscopic and robotic approach in multicenter cohort studies
- Evaluation of surgery with vascular resection and reconstruction in locally advanced tumors in multicenter cohort studies

## Perioperative oncological treatment

- Evaluation of the impact of neoadjuvant therapy on improving resectability and R0 rates particularly in borderline and locally-advanced disease in prospective, controlled studies
- Evaluation of adjuvant chemotherapy in the pCCA subgroup of cholangiocarcinoma, with a focus on patients with high-risk features (ie, patients with R1 resection status, or N+ disease)
- Evaluation of the relative contribution of postoperative radiotherapy to chemotherapy, with a focus on patients with high-risk features (i.e., patients with R1 resection status, or N+ disease)
- Evaluation of perioperative targeted or immunotherapy, including stratification for patients with primary sclerosing cholangitis
- Identification of the optimal time interval between neoadjuvant therapy and surgery
- Evaluation of radiotherapy in local disease recurrence

**TABLE 3.** (continued)

## Transplantation

- Evaluation of the need for neoadjuvant therapy in the transplant setting
- Identification of optimal neoadjuvant treatment protocols, including stratification for patients with primary sclerosing cholangitis
- Identification of predictors of tumor recurrence post-liver transplantation
- Comparison of liver transplantation and conversion surgery in responders to neoadjuvant treatment with initially unresectable disease

## Outcomes and reporting

- Implementation of large-scale national and international registries encompassing all tumor stages and treatments
- Standardized reporting of surgical outcomes in line with existing consensus recommendations
- Standardized reporting of patient-centered outcomes, including Quality of Life, patient satisfaction, and patient-reported metrics (ie, PROM, PREM)
- Evaluation of disease-specific adaptations to existing patient-reported metric through real-world, multi-stakeholder analysis
- Standardized reporting of histopathological evidence of response to neoadjuvant and adjuvant therapy
- Standardized reporting of completion rates for neoadjuvant and adjuvant therapy
- Standardized reporting of treatment-related deaths at 90 days following neoadjuvant and adjuvant therapy
- Integration of novel biomarkers (including ctDNA monitoring) and translational research in clinical studies
- Standardized reporting of follow-up with adherence to procedure-specific follow-up periods

ctDNA indicates circulating tumor DNA; MRI indicates magnetic resonance imaging; pCCA, perihilar cholangiocarcinoma; PREM, patient-reported experience Measure; PROM, patient-reported outcome measure.

expert opinion rather than empirical evidence. While surgical major hepatectomy is currently established as the standard approach for curative treatment, its supporting body of evidence remains limited to observational studies with very few multicenter reports (level of evidence 4). Experience with complex scenarios like vascular resection varies considerably across institutions globally and lacks generalizability. Similarly, liver transplantation mainly relies on the experience of a few centers, with many considering such an approach futile. In contrast, systemic oncologic treatments benefit from multicenter RCTs. These trials, however, targeted pooled biliary tract cancer cohorts, rather than pCCA specifically. This remains a shortcoming as emerging evidence on genetic alterations in cholangiocarcinoma have clearly indicated that intrahepatic and extrahepatic subtypes represent distinct entities. In this context of uncertainties, adhering to the standardized Zurich-Danish format and a rigorous, unbiased, and balanced jury-based approach<sup>15</sup> was critical to ensure credible recommendations, which reflect both the best available evidence and collective expert judgment.

As a countermeasure, the consensus process intends to globally align research efforts and clinical practice. Such collaborative intervention has proven beneficial in a previous highly complex and heavily debated liver diseases and therapies, such as in ALPPS.<sup>259</sup> An expert consensus conference in the procedure's early adoption phase was able to identify key technical adaptations and risk adjustments to dramatically improve outcomes. The implementation of an early international ALPPS registry<sup>260</sup> played a key role in

this development. Also, a recent consensus work on robotic HPB surgery<sup>18</sup> issued a call for caution and safety, strongly advocating for proper training and credentialing, particularly related to conversion to open surgery. Similarly, the current Consensus effort recognized that multidisciplinary expertise at every stage of pCCA diagnosis and treatment is critical to ensure both safety and appropriate therapy. This requires a bundle of tailored perioperative measures and protocols—carved out by experts and the jury—to enhance accuracy of diagnosis and staging, improve surgical resectability, and optimize perioperative patient management and oncological treatments. A main take-home message to be delivered to the clinical and surgical community remains that pCCA treatment must be centralized to high-volume centers fully equipped to deliver the entire palette of therapeutic options tailored to the patient's needs, and that every effort must be made to provide these measures in a timely manner without compromising further assessment and treatment.

Finally, critically assessing the impact of a consensus conference on clinical practice is essential to ensure that it translates into meaningful advancements. To this end, the implementation of recommendations must be continuously evaluated through standardized reporting of clinical outcomes and systematic reviews of the literature. As the identified research gaps are progressively addressed, periodic reassessments through follow-up consensus initiatives are necessary. Such an iterative process ensures sustained improvements in patient care and scientific progress.

In summary, this Consensus4pCCA endeavor represents a unique commitment of international multidisciplinary experts, an impartial jury, and a dedicated audience to collectively harmonize global treatment strategies for pCCA patients. This collective effort to bridge the gap between expert opinions and clinical evidence holds great promise to improve patient outcomes in the future, although many challenges remain to be overcome.

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