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Supplementary information

Cholangiocarcinoma 2026: status quo, unmet needs and priorities

In the format provided by the authors and unedited

Supplementary information

Expert Consensus Document Cholangiocarcinoma 2026: *Status Quo*, unmet needs and priorities

Supplementary Table 1. Delphi panelists

Name	Country	Background	Role
Abel Sanchez	Guatemala	Gastroenterologist	Consortium
Adelaida La Casta	Spain	Oncologist	Consortium
Aldo J. Montano-Loza	Canada	Hepatologist	Consortium
Alejandro Forner	Spain	Hepatologist	Steering
Alessandra Elvevi	Italy	Gastroenterologist	Consortium
Alessandro Parisi	Italy	Oncologist	Consortium
Alexander Link	Germany	Gastroenterologist	Consortium
Ana Landa-Magdalena	Spain	Oncologist	Consortium
Ana Lleo	Italy	Hepatologist	Steering
Andres Cardenas	Spain	Hepatologist	Steering
Andres Munoz	Spain	Oncologist	Consortium
Angela Lamarca	Spain	Oncologist	Steering
Anna Saborowski	Deutschland	Gastroenterologist	Steering
Anthony Turpin	France	Oncologist	Consortium
Anu Ustav	Estonia	Oncologist	Consortium
Apinya Jusakul	Thailand	Basic Scientist	Consortium
Arndt Vogel	Germany	Hepatologist	Steering
Arun Valsan	India	Hepatologist	Consortium
Bas Groot Koerkamp	Netherlands	Surgeon	Steering
Benjamin Dwyer	Australia	Basic Scientist	Consortium
Benjamin Goeppert	Germany	Pathologist	Steering
Bogdan S. Ungureanu	Romania	Gastroenterologist	Consortium
Bruno Sangro	Spain	Hepatologist	Consortium
Cédric Coulouarn	France	Basic Scientist	Steering
Chiara Braconi	United Kingdom	Oncologist	Core team
Chiara Raggi	Italy	Basic Scientist	Steering
Christoph Schramm	Germany	Hepatologist	Consortium
Cindy Neuzillet	France	Gastroenterologist	Consortium
Constantino Fondevila	Spain	Surgeon	Consortium
Cristina Dopazo	Spain	Surgeon	Steering
David James Pinato	United Kingdom	Oncologist	Consortium
David Malka	France	Hepatogastroenterologist	Consortium
Diego Francesco Calvisi	Germany	Basic Scientist	Steering
Domingo Balderramo	Argentina	Gastroenterologist	Consortium
Elide Gutierrez	Spain	Oncologist	Consortium
Elisa Lozano Esteban	Spain	Basic Scientist	Consortium
Emmanuel Boleslawski	France	Surgeon	Consortium
Enrique Carrera Estupinan	Ecuador	Hepatologist	Consortium
Ernesto Sparrelid	Sweden	Surgeon	Consortium

Eugenio Gaudio	Italy	Basic Scientist	Consortium
Fatima Higuera De La Tijera	Mexico	Hepatologist	Consortium
Flavio Rocha	USA	Surgeon	Consortium
Florence Troisfontaine	Belgium	Oncologist	Consortium
Francesca Ratti	Italy	Surgeon	Consortium
Frank Lammert	Deutschland	Gastroenterologist	Consortium
Gianpaolo Vidili	Italy	Hepatologist	Consortium
Gonzalo Sapisochin	Canada	Surgeon	Consortium
Gregory B. Lesinski	USA	Immunologist	Consortium
Gregory Gores	USA	Hepatologist	Consortium
Guido Carpino	Italy	Basic Scientist	Steering
Hannes Jansson	Sweden	Surgeon	Consortium
Hassan Malik	United Kingdom	Surgeon	Consortium
Heinz-Josef Klümpen	Netherlands	Oncologist	Steering
Helen Morement	United Kingdom	Patient Representative	Steering
Jan Philipp Jonas	Switzerland	Surgeon	Consortium
Javier Diaz Ferrer	Peru	Hepatologist	Consortium
Javier Vaquero	Spain	Basic Scientist	Consortium
Jean Charles Nault	France	Hepatologist	Steering
Jens U. Marquardt	Germany	Hepatologist	Consortium
Jesper B. Andersen	Denmark	Basic Scientist	Steering
Jesus Banales	Spain	Basic Scientist	Core team
Joana Espírito Santo	Portugal	Hepatologist	Consortium
John Bridgewater	United Kingdom	Oncologist	Steering
Jorge Adeva	Spain	Oncologist	Consortium
Joris Erdmann	Netherlands	Surgeon	Consortium
Jose J.G. Marin	Spain	Basic Scientist	Consortium
Juan Carlos Roa	Chile	Pathologist	Consortium
Juan Valle	USA	Oncologist	Steering
Juli Busquets	Spain	Surgeon	Consortium
Julien Edeline	France	Oncologist	Steering
Juozas Kupcinskas	Lithuania	Gastroenterologist	Consortium
Krzysztof Zieniewicz	Poland	Surgeon	Consortium
Lara Heij	Germany	Pathologist	Consortium
Laura Goff	USA	Oncologist	Consortium
Laura Izquierdo	Spain	Basic Scientist	Consortium
Leonardo G. Da Fonseca	Brazil	Oncologist	Consortium
Lorenza Rimassa	Italy	Oncologist	Steering
Luca Fabris	Italy	Hepatologist	Steering
Luca Maroni	Italy	Gastroenterologist	Consortium
Luis Bujanda	Spain	Gastroenterologist	Consortium

Luke Boulter	United Kingdom	Basic Scientist	Steering
Mairead McNamara	United Kingdom	Oncologist	Consortium
Marco Carbone	Italy	Hepatologist	Consortium
Marco Marzioni	Italy	Gastroenterologist	Consortium
Marco Rengo	Italy	Radiologist	Consortium
Maria Jesus Perugorria	Spain	Basic Scientist	Steering
Maria Melanie Deutsch	Greece	Hepatologist	Consortium
Mariano Ponz-Sarvise	Spain	Oncologist	Consortium
Mario Strazzabosco	USA	Hepatologist	Consortium
Markus Peck-Radosavljevic	Austria	Hepatologist	Consortium
Massimiliano Cadamuro	Italy	Basic Scientist	Consortium
Massimiliano Salati	Italy	Oncologist	Consortium
Massimo Colombo	Italy	Hepatologist	Consortium
Matei Mandea	Romania	Gastroenterologist	Consortium
Mathew Vithayathil	United Kingdom	Hepatologist	Steering
Mathias Heikenwälder	Germany	Basic Scientist	Steering
Matias A. Avila	Spain	Basic Scientist	Consortium
Matthias Evert	Germany	Pathologist	Consortium
Mina Komuta	Japan	Pathologist	Consortium
Mitesh Borad	USA	Oncologist	Consortium
Mohamed Bouattour	France	Hepatologist	Consortium
Mohamed El-Kassas	Egypt	Hepatologist	Consortium
Monica Isabel Meneses Medina	Mexico	Oncologist	Consortium
Monica Niger	Italy	Oncologist	Consortium
Monique Verstegen	Netherlands	Basic Scientist	Consortium
Nabeel Bardeesy	USA	Basic Scientist	Consortium
Nilofer Azad	USA	Oncologist	Consortium
Olivier Detry	Belgium	Surgeon	Consortium
Olivier Scatton	France	Surgeon	Consortium
P. Martin Padilla-Machaca	Peru	Gastroenterologist	Consortium
Patricia Aspichueta	Spain	Basic Scientist	Steering
Paula Olaizola	United Kingdom	Basic Scientist	Steering
Pedro M. Rodrigues	Spain	Basic Scientist	Core team
Pilar Acedo	United Kingdom	Basic Scientist	Consortium
Pim B. Olthof	Netherlands	Surgeon	Consortium
Piotr Milkiewicz	Poland	Hepatologist	Consortium
Rachel Guest	United Kingdom	Surgeon	Consortium
Rachna Shroff	USA	Oncologist	Consortium
Robert Montal	Spain	Oncologist	Consortium
Robin Kate Kelley	USA	Oncologist	Consortium

Rocio Macias	Spain	Basic Scientist	Steering
Ruidong Xue	China	Basic Scientist	Consortium
Sergio Gradilone	USA	Basic Scientist	Consortium
Shahid A. Khan	United Kingdom	Hepatologist	Steering
Shishir K. Maithel	USA	Surgeon	Consortium
Silvestre Vicent Cambra	Spain	Basic Scientist	Consortium
Silvia Affo	Spain	Basic Scientist	Steering
Siwanon Jirawatnotai	Thailand	Basic Scientist	Consortium
Stacie Lindsey	USA	Patient Representative	Steering
Stefano Caruso	France	Basic Scientist	Consortium
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Tian V. Tian	Spain	Pathologist	Consortium
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Tom Lüdde	Germany	Hepatologist	Steering
Trine Folseraas	Norway	Hepatologist	Steering
Tudor Mocan	Romania	Gastroenterologist	Consortium
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Umair Mahmood	United Kingdom	Clinical researcher	Consortium
Umberto Cillo	Italy	Surgeon	Consortium
Vera Megdanova	Bulgaria	Oncologist	Consortium
Victor Lopez-Lopez	Spain	Surgeon	Consortium
Vincenzo Cardinale	Italy	Gastroenterologist	Steering

The **Core team** includes the promotors of this project (JMB, PMR and CB). **Steering committee** indicates all co-authors of the review, and **Consortium members** contributed to the consensus by filling in the Delphi questionnaire. The consortium members are experts that were invited to fill questionnaire and are listed as one co-author “International CCA Consortium”.

Supplementary Table 2. Age-standardised (WHO World Standard population[1]) mortality rates[2,3] for intrahepatic and extrahepatic cholangiocarcinoma (ICD-10 codes C22.1 and C24.0) per 100,000 person-years.

	Year							
	2011	2013	2015	2017	2019	2021	AAPC %	% change
Europe								
Austria	2.20	2.39	2.30	2.38	2.08	2.28	0.53	3.49
Belgium	1.58	1.61	1.65	1.51	1.84	2.01	2.69	27.13
Bulgaria		0.31	0.48	0.47	0.41	0.53	8.48	69.38
Croatia	1.39	1.62	1.69	1.53	1.65	1.79	2.73	28.33
Cyprus	1.20	1.76	0.80	1.36	1.32	1.44	6.82	19.49
Czech Republic	0.93	1.18	0.92	1.12	1.15	1.04	2.01	12.27
Denmark	0.84	1.06	1.38	1.30	1.44	1.69	7.93	102.12
Estonia	0.89			1.48	2.05	2.14	9.73	141.47
France	1.57	1.77	1.80	1.91	1.88	1.93	2.16	22.92
Germany	1.79	1.91	1.97	2.28	2.30		3.30	28.42
Greece			1.29	1.28	1.26	1.26	-0.39	-2.31
Hungary	0.69	1.64	1.90	1.83	1.94	1.64	13.88	136.36
Ireland	2.36	2.43	2.09				-2.75	-11.48
Italy	1.14	1.20	1.22	1.22	1.34	1.29	1.23	12.37
Latvia	0.85	1.10	1.21	1.26	1.15	1.46	6.17	71.91
Lithuania	1.21	0.82	1.25	1.20	1.72	1.47	4.51	21.05
Luxembourg	1.66	2.59	1.69	1.75	1.77	1.61	1.66	-3.25
Netherlands	1.19	1.32	1.60	1.75	1.75	2.00	5.61	68.58
Norway	1.39	1.19	1.47				2.27	5.82
Poland	0.33	0.33	0.39	0.41	0.45	0.42	2.49	25.70
Portugal	1.29	1.75	1.65	1.79	1.99		6.13	53.58
Republic of Moldova	0.28	0.39	0.35	0.47		0.38	5.59	38.35
Romania	0.57	0.68	0.76	0.85	0.82		5.05	45.15
Slovakia		1.28		1.04	1.14	1.00	-4.24	-22.17
Spain	1.59	1.72	1.81	1.94	2.00	1.97	2.20	23.76
Sweden	1.29	1.64	1.64	1.60	1.74	2.01	4.93	56.44
Switzerland	1.61	1.70	1.71	1.66	1.56	1.42	-1.17	-11.77
United Kingdom	1.74	1.99	2.02	2.12	2.20	2.37	3.24	36.32
Asia								
Israel	1.06	0.97	1.13	1.01	1.09	1.03	-0.03	-2.99
Hong Kong	2.59	2.55	2.51	2.43	2.25	2.43	-0.55	-5.99
Japan	3.49	3.35	3.25	3.15	3.01	2.96	-1.62	-15.18
Republic of Korea	4.87	4.79	4.83	5.10	5.10	4.87	0.03	0.00
Singapore		2.14	1.83	2.09	1.35	1.38	-4.19	-35.63
Sri Lanka	0.31	0.26	0.30		0.43		0.38	36.44
Thailand				4.27	4.40	3.87	-2.25	-9.40
Türkiye	0.60	0.77	0.72	0.79	0.63	0.49	-1.22	-19.08
North America								
Canada	1.28	1.39	1.66	1.73	1.78	1.89	4.17	
Costa Rica	1.24	1.46	1.68	1.68	1.53	1.64	3.11	32.30
Cuba	0.32	0.42	0.36	0.40	0.27	0.25	-1.43	-22.67
Guatemala	0.34	0.26	0.42	0.37	0.26	0.41	5.28	20.02
Mexico	0.64	0.70	0.71	0.77	0.72	0.69	0.82	7.46
Nicaragua	0.60	0.54	0.86	0.71	0.94	1.07	7.90	79.40
Panama	0.83	0.24	0.89	1.29	1.25	1.12	22.75	34.48
United States of America	1.13	1.22	1.30	1.40	1.49	1.57	3.32	37.94
South America								
Argentina	0.23	0.27	0.27	0.25	0.32	0.30	2.97	27.82
Brazil	0.85	0.79	0.84	0.82	0.76	0.74	-1.27	-12.58
Chile	0.42	0.81	1.02	1.05	1.21	1.20	13.61	184.99

Colombia	0.76	0.77	0.90	0.91	0.91	0.96	2.47	26.19
Ecuador	0.57	0.81	1.06	0.74	0.84	0.86	5.96	51.35
Paraguay	0.17	0.40	0.42	0.44	0.40	0.58	17.38	231.83
Peru	0.35	0.44	0.41	0.56	0.81		12.47	130.73
Uruguay		0.51	0.38	0.67	0.69	1.14	14.80	123.56
Venezuela	0.53	0.41	0.47				-1.83	-10.21
Oceania								
Australia	1.58	1.77	1.91	1.94	2.12	2.13	3.15	35.04
New Zealand	1.49	1.56	1.57	1.63			1.54	9.44

AAPC, average annual percentage change

Supplementary Table 3. Most relevant genetic mutations in histologic iCCA subtypes

Reference	Molecular Alteration	SBD	LBD	Fisher's exact test
Hayashi A, *et al.* 2016[4]	*KRAS* *IDH1/2*	1/50 (2%) 21/53 (39.6%)	10/34 (29.4%) 0/34 (0%)	**0.0004** **0.0001**
Tsai JH, *et al.* 2012[5]	*KRAS*	0/34 (0%)	9/32 (28.1%)	**0.0008**
Akita M, *et al.* 2019[6]	*KRAS* *IDH1/2*	6/36 (17%) 4/36 (12%)	3/22 (14%) 0/22 (0%)	>0.9999 0.2868
Liau JY, *et al.* 2014[7]	*KRAS* *IDH1/2*	1/76 (1.3%) 13/76 (17%)	23/98 (23%) 5/95 (5.3%)	**<0.0001** **0.0218**
Wang T, *et al.* 2019[8]	*IDH1/2*	29/72 (40%)	0/9 (0%)	**0.0229**
Ma B, *et al.* 2020[9]	*IDH1/2*	20/103 (19%)	1/27 (3.7%)	0.0740
Li Z, *et al.* 2023[10]	*FGFR2*	20/89 (22%)	0/101 (0%)	**<0.0001**
Jeon Y, *et al.* 2023[11]	*KRAS* *IDH1/2* *FGFR2* *TP53*	1/32 (3.1%) 10/32 (31.3%) 4/32 (12.5%) 3/32 (9.4%)	3/22 (13.6%) 1/22 (4.5%) 0/22 (0%) 3/22 (13.6%)	0.2927 **0.0190** 0.1368 0.6784
Total	***KRAS*** ***IDH1/2*** ***FGFR2***	**9/228 (3.9%)** **Range: 0 – 17 %** **98/372 (26.3%)** **Range: 12 – 40%** **24/121 (19.8%)** **Range: 12 – 22%**	**48/208 (23%)** **Range: 14 – 29%** **7/209 (3.3%)** **Range: 0 – 5.3%** **0/123 (0%)** **Range: /**	**<0.0001** **<0.0001** **<0.0001**

The number of patients with a given molecular alteration in different iCCA subtypes was extrapolated from each of the mentioned original articles. All the retrieved data were included in the table (number of patients and percentage). The total number of patients with a given mutation was obtained by the sum of the patients included in all considered studies and Fisher's exact test was calculated.

Supplementary References

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Supplementary Data

DELPHI QUESTIONNAIRE

Dear panelists,
According to your renown expertise in the study of cholangiocarcinoma (CCA), you are invited to participate in a Delphi Questionnaire to establish expert consensus and define research priorities in the field.

We ask you now to complete the survey, that should take between 15-30 min. To do this, we will first ask for your consent to participate in this study and request some very basic details: name, email address, location and your background/speciality. Please note that this information is required only to confirm your participation in the Delphi Questionnaire. Once the survey is complete and your participation is registered, we will delete your name and email address from the research record, and your answers will be treated anonymously.

We will ask you to answer some questions related to “Epidemiology and Risk Factors”, “Clinical presentation: diagnosis and staging”, “Genetics”, “Tumour biology”, “Biomarkers”, “Treatment”, “Supportive care” and “Future research” divided in 8 sections. You may only provide **one single answer** to all the questions. In case you some of the questions fall outside of your expertise and yo don’t feel qualified to answer some of the them, please select the “Unable to comment” answer. We are planning to conduct one round of questions but in case we need, we may conduct a second round of the Delphi Questionnaire.

Thank you very much for your contribution.

PERSONAL DATA* (mandatory)

Name:

E-mail address:

Location:

Background/speciality:

- *Basic Scientist*
- *Hepatologist*
- *Gastroenterologist*
- *Oncologist*
- *Surgeon*
- *Pathologist*
- *Radiologist*
- *Geneticist*
- *Immunologist*
- *Endoscopist*
- *Patient representative*
- *Other (please specify)*

I. EPIDEMIOLOGY AND RISK FACTORS

1) *Based on the potential differences in aetiology, pathogenesis, incidence and prognosis, since January 1st 2022, the latest version of ICD coding (ICD-11) introduced specific and separate codes for intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA). Should this new classification be considered in all hospitals worldwide and avoid the use of intra- or extrahepatic (eCCA)?*
    - Agree
    - Disagree
    - Unable to comment

2) *Should the term extrahepatic CCA exclude malignant neoplasms of the gallbladder, the cystic duct and the ampulla of Vater?*
    - Yes, they should be named “Biliary tract Cancers”
    - No, they can be included under the umbrella of eCCA
    - Unable to comment

3) *The record of patients with CCA should include the information on whether they are considered “sporadic” (without any known risk factors) or if they are associated with known risk factors (e.g., liver cirrhosis and its aetiology, primary sclerosing cholangitis (PSC), congenital hepatic fibrosis (CHF), biliary stones, choledochal cysts).*
    - Agree
    - Disagree
    - Unable to comment

4) *CCA is considered to represent 10-15% of all primary liver tumours, 3% of gastrointestinal cancers and accounts for 2% of cancer-related deaths. Nevertheless, these data might be underestimated due to systematic errors in data retrieval, diagnosis and coding.*
    - Agree
    - Disagree
    - Unable to comment

5) *The reported worldwide increase in iCCA incidence may be linked to an increase awareness in cancers previously misclassified as Cancer of Unknown Primary (CUP) during the last years .*
    - Agree
    - Disagree
    - Unable to comment

6) *The surveillance recommendations of patients with PSC for early CCA detection is suboptimal and may benefit from further research.*
    - Agree
    - Disagree
    - Unable to comment

7) *The current clinical follow-up pipeline for patients with liver cirrhosis has been designed for the early detection of HCC; however, it may also be effective for the early detection of iCCA too and does not require changes.*
    - Agree
    - Disagree*
    - Unable to comment
    - ** Suggested changes…*

8) *The current evidence of the protective effect of aspirin and/or statins for CCA development in the general population is strong enough to advise clinical implementation.*
    - Yes, both aspirin and statins should be recommended
    - Yes, but only aspirin should be recommended
    - Yes, but only statins should be recommended
    - No, none should be recommended due to the lack of strong evidence. More research is needed.
    - Unable to comment

II. CLINICAL PRESENTATION: DIAGNOSIS AND STAGING

9) *Histological assessment is required for definitive diagnosis of CCA.*
    - Agree
    - Disagree
    - Unable to comment

10) *A histological analysis should provide information on diagnosis and tumor features (differentiation grade, vascular invasion, among others), always ensuring that enough tumour tissue is available for molecular profiling to guide personalised therapy.*
    - Agree
    - Disagree
    - Unable to comment

11) *The identification of an adenocarcinoma with biliary markers, in the absence of another primary tumours (colorectal cancer or other gastrointestinal cancers), is enough to confirm CCA diagnosis.*
    - Agree
    - Disagree
    - Unable to comment

III. GENETICS

12) *Tumour molecular testing is currently recommended by international guidelines in patients with advanced disease. Next-generation sequencing (NGS) should be performed in tumour tissue as first choice.*
    - Agree
    - Disagree
    - Unable to comment

13) *NGS in circulating tumour DNA (ctDNA) in blood may be considered when tumour tissue is not available to identify druggable molecular alterations.*
    - Agree
    - Disagree
    - Unable to comment

14) *When a biopsy is not feasible or when cytology does not provide enough material, ctDNA can be used for diagnosis.*
    - Agree
    - Disagree
    - Unable to comment

15) *Fluorescent in-situ hybridization (FISH) is an appropriate alternative for the detection of FGFR2-fusions only if NGS is not feasible.*
    - Agree
    - Disagree
    - Unable to comment

16) *Immunohistochemistry is an appropriate first method to detect ERBB2 amplifications.*
    - Agree
    - Disagree
    - Unable to comment

17) *Immunohistochemistry is an appropriate first method to detect mismatch repair (MMR) deficiency.*
    - Agree
    - Disagree
    - Unable to comment

18) *Molecular profiling impacts on the clinical-decision making beyond the indication of targeted therapies (for instance, by identifying distinct molecular subtypes).*
    - Agree
    - Disagree
    - Unable to comment

19) *Molecular profiling of CCA should be done as reflex test initiated by the following a histological diagnosis of CCA in patients with advanced disease eligible for treatment.*
    - Agree
    - Disagree
        - If you disagree, in which cases?
    - Unable to comment

IV. TUMOUR BIOLOGY

20) *To meet the anabolic demands, malignant cells and cellular components of the microenvironment tend to rewire their metabolic pathways. Although different types of malignant cells share this phenomenon, there is a great intracellular variability of these metabolic patterns.*
    - Agree
    - Disagree
    - Unable to comment

21) *Developing compounds that target key players of mitochondrial pathways may be promising in CCA.*
    - Agree
    - Disagree
    - Unable to comment

22) *CCAs are highly desmoplastic and hypovascularized tumours. Stroma content and composition affect the progression, evolution and response to systemic therapies.*
    - Agree
    - Disagree
    - Unable to comment

V. BIOMARKERS

23) *For their clinical implementation, biomarkers should be prospectively validated for the intended purpose (e.g. diagnostic, prognostic, predictive, or pharmacodynamic) in international cohorts including individuals with different risk factors and ethnicities, and compared to appropriate control groups.*
    - Agree
    - Disagree
    - Unable to comment

24) *Serum CA19-9 and CEA levels are not accurate biomarkers particularly for the detection of small CCA lesions (early tumor stages).*
    - Agree
    - Disagree
    - Unable to comment

25) *Serum CA19-9 and CEA levels should be used as comparators for the development of novel biomarkers for the early diagnosis of CCA*
    - Agree
    - Disagree
    - Unable to comment

26) *Serum CA19-9 levels (in known secretors and in the absence of biliary obstruction) have independent prognostic value on overall survival for patients and should be balanced between groups in clinical trial design.*
    - Agree
    - Disagree
    - Unable to comment

27) *Serum CA19-9 levels correlate with radiological response to systemic therapies and should be monitored clinically during treatment.*
    - Agree
    - Disagree
    - Unable to comment

28) *Serum AFP should be tested and monitored in cases of iCCA arising from liver cirrhosis*
    - Agree
    - Disagree
    - Unable to comment

29) *There are biomarkers that support systemic therapy decision making.*
    - Agree
    - Disagree
    - Unable to comment

VI. TREATMENT

30) *Consensus on radiological criteria for resectability of CCA is needed.*
    - Agree
    - Disagree
    - Unable to comment

31) *In patients with a cirrhotic liver presenting an iCCA single tumour δ2cm liver transplantation can be a therapeutic option*.
    - Agree
    - Disagree
    - Unable to comment

32) *Liver Transplantation for perihilar cholangiocarcinoma (pCCA) may be a therapeutic option in patients with unresectable pCCA, δ3cm in radial size, and no extrahepatic disease or lymph node spread.*
    - Agree
    - Disagree
    - Unable to comment

33) *In the era of precision medicine, chemotherapy is of benefit for all patients with advanced CCA.*
    - Agree
    - Disagree

- Unable to comment

34) *PSC and PBC are immune-mediated liver diseases; the triple combination of gemcitabine, cisplatin and immunotherapy in first-line should be also considered in patients with CCA arising in these backgrounds considering the risk-benefit.*
    - Agree
    - Disagree
    - Unable to comment

35) *FOLFOX is a chemotherapy regimen to be considered in patients who progressed to first line treatment, in absence of druggable alterations, after weighing up the potential risks and benefits.*
    - Agree
    - Disagree
    - Unable to comment

36) *Understanding the effect of chemotherapy and immunotherapy in CCAs with specific actionable genetic alterations may impact clinical decisions.*
    - Agree
    - Disagree
    - Unable to comment

37) *dMMR/MSI-H is a good predictive biomarker of response to immunotherapy in CCA.*
    - Agree
    - Disagree
    - Unable to comment

38) *HER2 overexpression and/or amplification is a good predictive biomarker of response to anti-HER2 regimens.*
    - Agree
    - Disagree
    - Unable to comment

39) *Patients with CCA and $BRAF^{V600E}$ mutation previously treated with ε1 line of systemic therapy should be considered for treatment with dabrafenib-trametinib, when available.*
    - Agree
    - Disagree
    - Unable to comment

40) *Molecular testing of advanced biliary tract cancer should be panel-based and broader than for known actionable alterations for which therapies are already available in order to be able to consider new targeted therapies in development in the setting of clinical trials*
    - Agree
    - Disagree
    - Unable to comment

41) *Progression free survival (PFS) is an appropriate surrogate marker of treatment response in clinical trials with patients with CCA.*
    - Agree
    - Disagree
    - Unable to comment

42) *Progression free survival (PFS) should be sufficient as a primary end-point in clinical trials with patients with CCA.*
    - Agree
    - Disagree
    - Unable to comment

43) *Overall survival (OS) should be the primary end-point in clinical trials with patients with CCA.*
    - Agree
    - Disagree
    - Unable to comment

44) *Single-arm clinical trials with targeted therapies could benefit from data of the natural course of matched patients obtained from international clinical registries for regulatory approval.*
    - Agree
    - Disagree
    - Unable to comment

45) *Treatment recommendations for patients with CCA should be based on discussions in multidisciplinary tumour boards.*
    - Agree
    - Disagree
    - Unable to comment

46) *Collection of biological samples should be pursued within clinical trials and clinical practice to improve understanding of the disease, the impact of therapies and ultimately improve patient outcomes.*
    - Agree
    - Disagree
    - Unable to comment

VII. SUPPORTIVE CARE

47) *Upon CCA diagnosis, psychological support should be considered.*
    - Agree
    - Disagree
    - Unable to comment

48) *Upon CCA diagnosis, dietary and nutrition counselling should be recommended.*
    - Agree
    - Disagree
    - Unable to comment

VIII. FUTURE RESEARCH

49) *Further research is needed to assess if patients-derived advanced 3D culture models (i.e., organoids, organ-on-a-chip, precision-cut liver slices, among others) can be used to tailor therapeutic approaches related to specific signalling pathways or altered processes.*
    - Agree
    - Disagree
    - Unable to comment

50) *Highly proliferative CCA cells rely on increased lipid and lipoprotein uptake and metabolization to support their growth. More research is needed to determine the clinical implications of these findings (i.e. diet advice; therapeutic manipulation).*
    - Agree
    - Disagree
    - Unable to comment

51) *Strategies aiming to modulate the CCA tumour immune microenvironment (TIME) deserve further investigations to expand therapeutic targets.*
    - Agree
    - Disagree
    - Unable to comment

52) *CCA classes identified by molecular and immune characterization have been proposed to be clinically relevant in terms of patient outcome. These molecular classifications should be clinically investigated in prospective trials.*
    - Agree
    - Disagree
    - Unable to comment

53) *Further research in biomarker for systemic therapy response is needed.*
    - Agree
    - Disagree
    - Unable to comment

54) *Clinical investigation of the role of neoadjuvant systemic treatment in non-metastatic CCA is needed.*
    - Agree
    - Disagree
    - Unable to comment

55) *Further clinical investigation is needed to identify the role of local therapy in CCA and their appropriate combination with systemic treatments.*
    - Agree
    - Disagree
    - Unable to comment

56) *The impact of systemic treatment according to the location of the CCA should be assessed in the future.*
    - Agree
    - Disagree
    - Unable to comment

57) *Investigation of the role of targeted therapies in first line is relevant in patients with advanced (unresectable or metastatic) disease.*
    - Agree
    - Disagree
    - Unable to comment

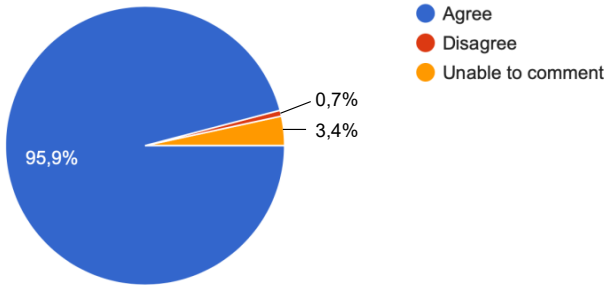
58) *The role of liquid biopsy to monitor tumour evolution during treatment should be investigated in prospective studies.*
    - Agree
    - Disagree
    - Unable to comment

59) *Predictive biomarkers of treatment response to immunotherapy are highly needed.*
    - Agree
    - Disagree
    - Unable to comment

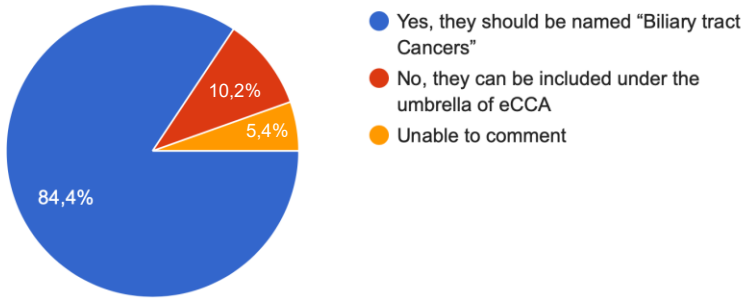
RESULTS FROM THE DELPHI QUESTIONNAIRE

I. EPIDEMIOLOGY AND RISK FACTORS

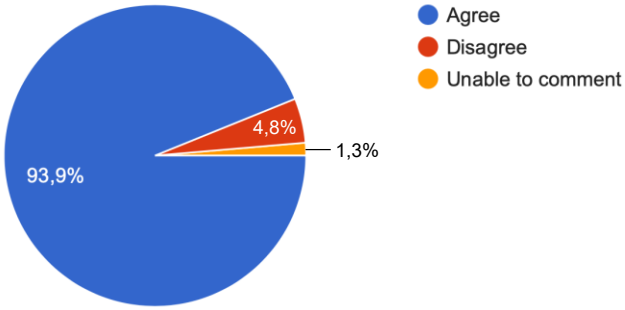
1) *Based on the potential differences in aetiology, pathogenesis, incidence and prognosis, since January 1st 2022, the latest version of ICD coding (ICD-11) introduced specific and separate codes for intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA). Should this new classification be considered in all hospitals worldwide and avoid the use of intra- or extrahepatic (eCCA)?*



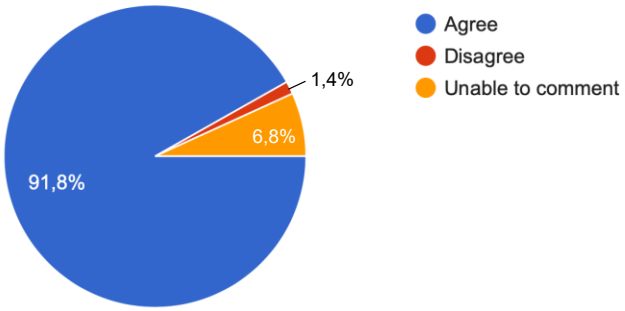
2) *Should the term extrahepatic CCA exclude malignant neoplasms of the gallbladder, the cystic duct and the ampulla of Vater?*
   - Yes, they should be named “Biliary tract Cancers”
   - No, they can be included under the umbrella of eCCA
   - Unable to comment



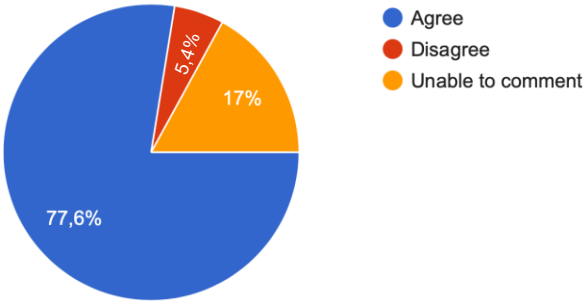
3) *The record of patients with CCA should include the information on whether they are considered “sporadic” (without any known risk factors) or if they are associated with known risk factors (e.g., liver cirrhosis and its aetiology, primary sclerosing cholangitis (PSC), congenital hepatic fibrosis (CHF), biliary stones, choledochal cysts).*
   - Agree
   - Disagree
   - Unable to comment



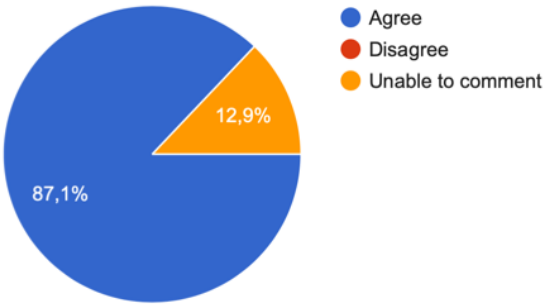
4) *CCA is considered to represent 10-15% of all primary liver tumours, 3% of gastrointestinal cancers and accounts for 2% of cancer-related deaths. Nevertheless, these data might be underestimated due to systematic errors in data retrieval, diagnosis and coding.*
    - Agree
    - Disagree
    - Unable to comment



5) *The reported worldwide increase in iCCA incidence may be linked to an increase awareness in cancers previously misclassified as Cancer of Unknown Primary (CUP) during the last years .*
    - Agree
    - Disagree
    - Unable to comment

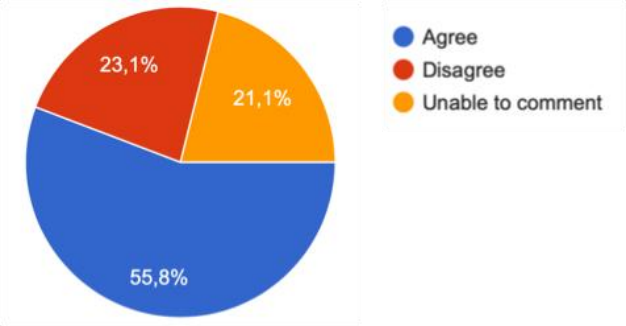


6) *The surveillance recommendations of patients with PSC for early CCA detection is suboptimal and may benefit from further research.*
    - Agree
    - Disagree
    - Unable to comment



7) *The current clinical follow-up pipeline for patients with liver cirrhosis has been designed for the early detection of HCC; however, it may also be effective for the early detection of iCCA too and does not require changes.*
    - Agree
    - Disagree*

- Unable to comment

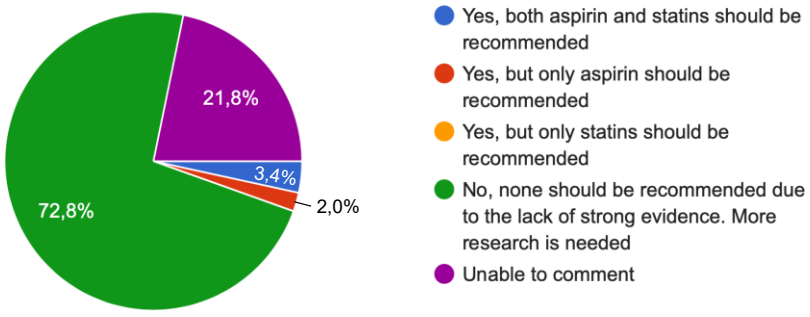


- ** Suggested changes:*
    - *Low level of evidence of efficiency (or insufficient efficiency); research needed, for instance the value (or absence of value) of adding CA19.9 to AFP.*
    - *Ultrasound may be effective in the early detection of mass-forming iCCA, but it may miss the early detection of periductal-infiltrating and intraductal-growing subtypes. The recommendation for performing an ultrasound every 6 months in patients with cirrhosis is weak, and although there is no evidence, MRCP could be considered in patients with additional risk factors for iCCA besides PSC.*
    - *Include lab screening for CA19.9 along with AFP.*
    - *The data on screening BTC in cirrhosis is lacking.*
    - *Ca 19.9.*
    - *Only AFP and US are measured for HCC. Need a CA 19-9 for CCA.*
    - *More frequent use of MRI/MRCP if any rise in ca19-9 or Liver enzymes.*
    - *The statement is misleading. the follow-up for HCC requires ultrasound as imaging modalities but this is not accurate for the "early" detection of CCA. MRCP should be considered in high risk CCA patients.*
    - *Substantial differences in clinical follow-up of cirrhosis patients and mainly ultrasound as modality, sometimes combined with AFP but not CA 19.9.*
    - *We may want to use different markers as part of the algorithm and consider exploring the use of ctDNA.*
    - *To plan pet-tc as a routine in cirrhotic patients.*
    - *There are no data to guide us in the policy to implement. A prospective study on this specific topic should be set up.*
    - *I consider liver US might be suboptimal as screening tool for iCCA. There is a need for better serum screening tests for iCCA.*
    - *Requires clarification, since not all patients with iCCA have an underlying liver cirrhosis. iCCA due to other aetiologies, cALD/MASH might require different approaches. Further research is required to validate the approach. Discordant guidelines regarding biomarkers (e.g. AFP) in international guidelines need to be considered and adjusted for iCCA accordingly.*
    - *Biology of HCC and iCCA are not the same and probably some iCCA may skip actual HCC follow up avoiding improving OS for some patients.*
    - *Unclear definition of population at risk and survival benefit for CCA diagnosis specifically.*
    - *We need more effective/accurate non-invasive screening in cirrhotic including blood-based biomarkers for both ICC and HCC.*
    - *iCCA might progress much faster than HCC and the follow-up intervals should possibly be adjusted. Particularly, as there are no good precursors that can be monitored, other*

than in HCC in which at least suspicious cirrhotic [dysplastic] nodules for HCC are available for follow-up.

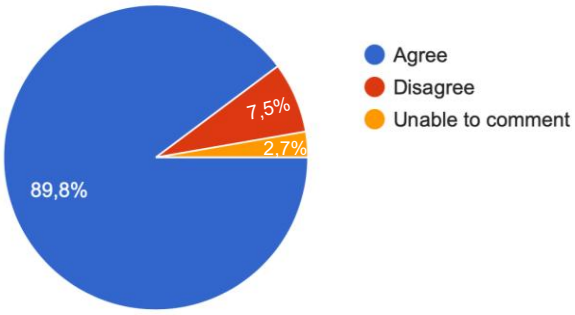
- *The small bile duct iCCA typically is a mass-forming tumour. In this case the ultrasound-based screening in liver cirrhosis could work. Instead, the large bile duct iCCA, less frequent in liver cirrhosis, with the exception of PSC, does not have a mass-forming growth and is not detected by ultrasound. A multimodal screening approach (consider also new algorithms of machine learning) for large bile duct iCCA is necessary.*
- *CEA and Ca19.9 may need to be added.*
- *Additional biomarkers should be considered in the screening programs.*
- *Include CA19-9.*
- *To test the role of liquid biopsy, besides EUS and RMN.*
- *Include CA19-9 and biopsy of hepatic lesions.*
- *Further studies are required to improve early detection of iCCA.*
- *More than half of HCC does occur in non-cirrhotic patients so does iCCA. liver cirrhosis-based follow-up its self needs to be re-considered.*
- *Radiologic criteria for diagnosis are different. Biopsy is needed to stablish diagnosis.*
- *Include CA19.9 and/or gama-glutamyl transferase may add sensitivity.*
- *When in doubt with the ultrasound follow-up, perform MRI.*
- *More enhancement for the role of MRI.*
- *Follow-up could include except of AFP also CA19-9.*
- *Specific biomarkers of cirrhotic patients that could progress to iCCA should be identified to early detect patients that might progress to iCCA.*
- *N/A (x2)*

8) *The current evidence of the protective effect of aspirin and/or statins for CCA development in the general population is strong enough to advise clinical implementation.*
   - Yes, both aspirin and statins should be recommended
   - Yes, but only aspirin should be recommended
   - Yes, but only statins should be recommended
   - No, none should be recommended due to the lack of strong evidence. More research is needed.
   - Unable to comment

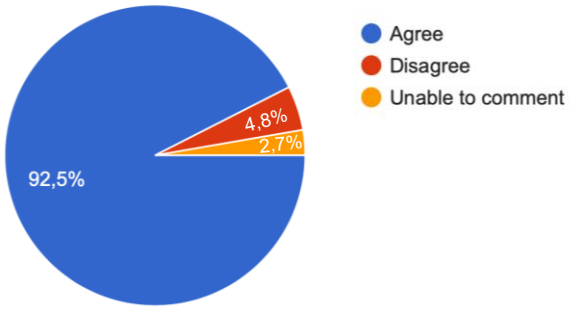


II. CLINICAL PRESENTATION: DIAGNOSIS AND STAGING

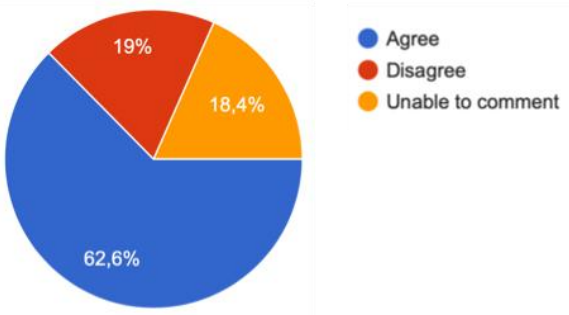
9) *Histological assessment is required for definitive diagnosis of CCA.*
   - Agree
   - Disagree
   - Unable to comment



10) *A histological analysis should provide information on diagnosis and tumor features (differentiation grade, vascular invasion, among others), always ensuring that enough tumour tissue is available for molecular profiling to guide personalised therapy.*
   - Agree
   - Disagree
   - Unable to comment

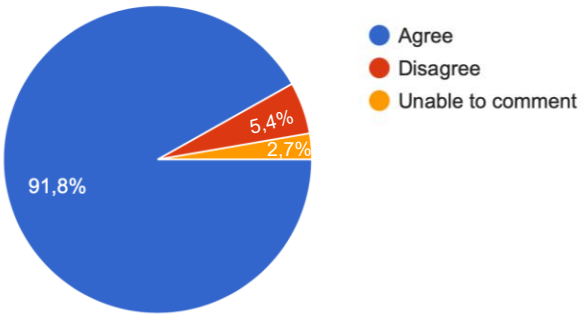


11) *The identification of an adenocarcinoma with biliary markers, in the absence of another primary tumours (colorectal cancer or other gastrointestinal cancers), is enough to confirm CCA diagnosis.*
   - Agree
   - Disagree
   - Unable to comment

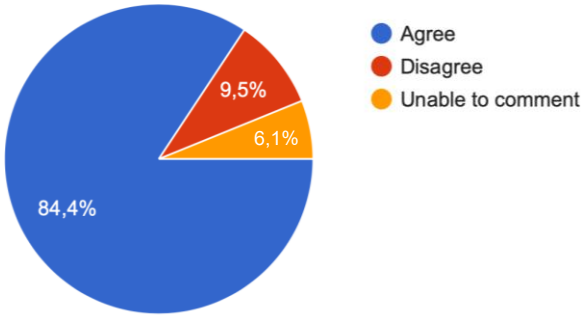


III. GENETICS

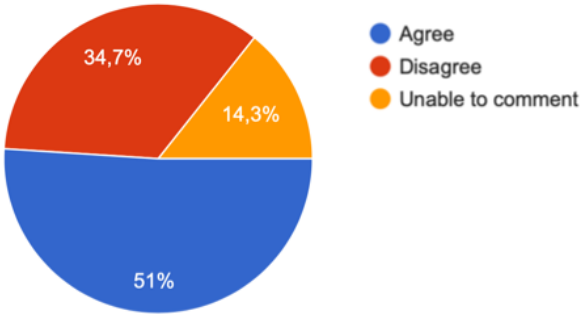
12) *Tumour molecular testing is currently recommended by international guidelines in patients with advanced disease. Next-generation sequencing (NGS) should be performed in tumour tissue as first choice.*
    - Agree
    - Disagree
    - Unable to comment



13) *NGS in circulating tumour DNA (ctDNA) in blood may be considered when tumour tissue is not available to identify druggable molecular alterations.*
    - Agree
    - Disagree
    - Unable to comment

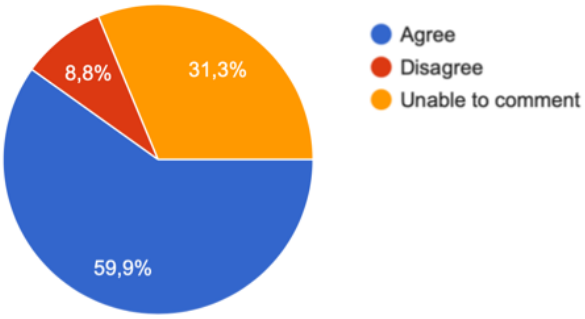


14) *When a biopsy is not feasible or when cytology does not provide enough material, ctDNA can be used for diagnosis.*
    - Agree
    - Disagree
    - Unable to comment



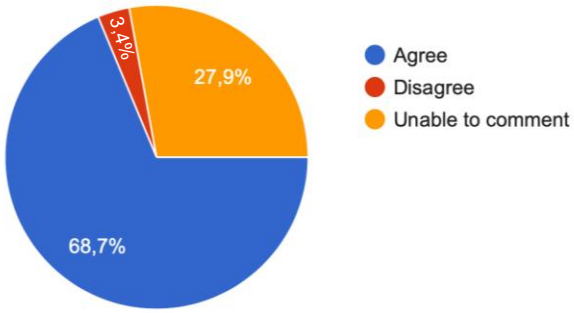
15) *Fluorescent in-situ hybridization (FISH) is an appropriate alternative for the detection of FGFR2-fusions only if NGS is not feasible.*

- Agree
- Disagree
- Unable to comment



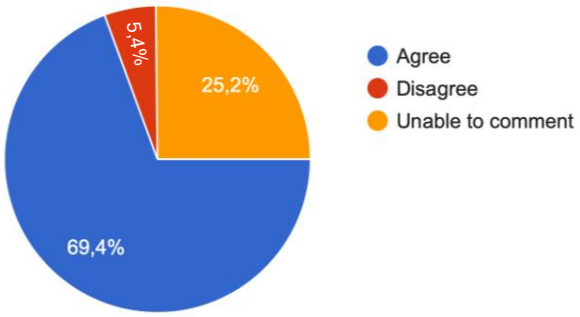
16) *Immunohistochemistry is an appropriate first method to detect ERBB2 amplifications.*

- Agree
- Disagree
- Unable to comment

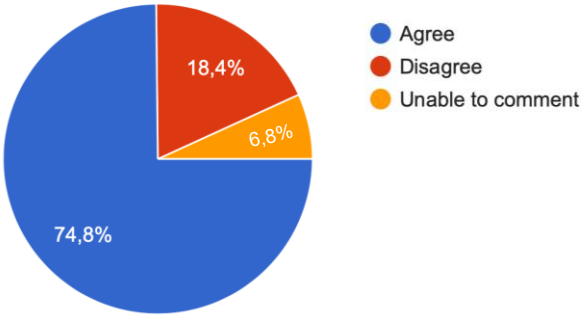


17) *Immunohistochemistry is an appropriate first method to detect mismatch repair (MMR) deficiency.*

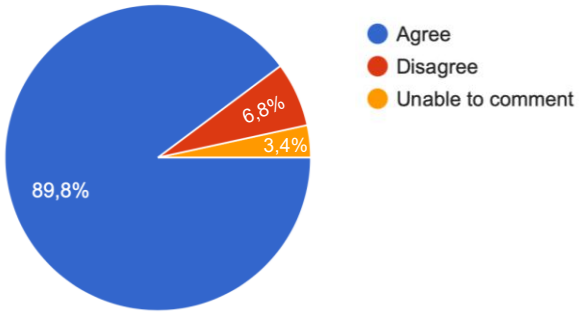
- Agree
- Disagree
- Unable to comment



18) *Molecular profiling impacts on the clinical-decision making beyond the indication of targeted therapies (for instance, by identifying distinct molecular subtypes).*
    - Agree
    - Disagree
    - Unable to comment



19) *Molecular profiling of CCA should be done as reflex test initiated by the following a histological diagnosis of CCA in patients with advanced disease eligible for treatment.*
    - Agree
    - Disagree*
    - Unable to comment



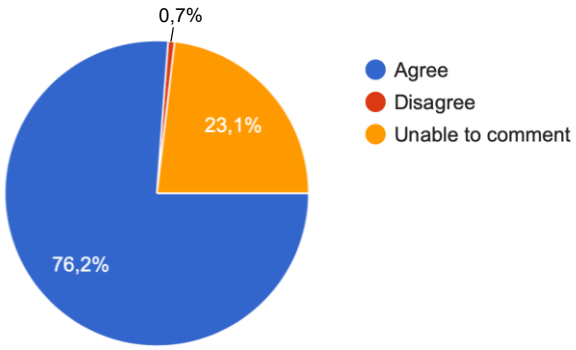
- *If you disagree, in which cases?
    - *I disagree with the fact that molecular information can be useful for treatment decisions beyond target therapy, today I think we don´t have enough data regarding prognostic data.*
    - *I think it is early to DIAGNOSE CCA with ctDNA, adds suspicion for sure. Not sure if Diagnosis.*
    - *Not enough data to validate ctDNA for diagnosis Prefer rebiospy for appropriate NGS rather than FISH (lower sensitivity) for FGFR2 fusion.*
    - *In nationwide studies, up to 50% of pCCA and iCCA patients never become adequately drained and fit for ANY treatment. Reflex molecular profiling would be a waste of money. Moreover, most patients don't become eligible for second-line treatment and treatments based on molecular profiling are not yet recommended in first-line. Finally, we should be humble about the OS benefit of all these new treatments. I haven't seen the RCTs showing a clinically relevant and statistically significant benefit in OS. I also disagreed on one of the questions on diagnosis. That section didn't offer a comment box. Therefore, my comment below: In section on diagnosis, I disagreed about requiring histological diagnosis, because this is often infeasible for pCCA without resection. And only 15% gets a resection. So with this strict requirement of histological diagnosis, this means that 85% of all patients with pCCA will not be registered as pCCA. Maybe a few more patients can be confirmed with biopsy of metastasis. But most patients have no mass or a small mass and are too frail for major liver surgery.*

- *There are no enough data to support the use of ctDNA to replace histology as diagnosis. ctDNA may provide misleading information.*
- *2L (in 1L is welcomed but not mandatory).*
- *Selected patients amenable to advanced treatment.*
- *In all answers regarding ctDNA, testing can help to support diagnostic pipeline. However, only positive results should be considered definitive. Negative results should trigger further testing/acquisition of material. Reflex testing is potentially efficient and appropriate but potentially problematic regarding re-imbursement for the general CCA population. Validity of this approach should be evaluated in specialized centers before general recommendation.*
- *Ideally NGS test should include MMR, HER2 amplification and FGFR2 fusion. HER2 amplification cannot be assessed by IHC in fact guidelines use HER2 (gastric/breast/colon) for protein over expression which may not always be caused by HER2 amplification at the DNA level.*
- *Only if fit treatment will be started.*
- *ctDNA cannot be reliably utilised for diagnosis.*
- *I think it should be done to all patients.*
- *The clinical impact of molecular profiling in the selection of targeted therapies.*
- *When a biopsy is not feasible, both diagnosis and molecular analysis should be conducted on surgical specimen if the patients is technically resectable in high suspicion of CCA.*
- *Reflex test means that it is done in all cases where pathology is consistent with CCA. I would say it has to be done in patients with advanced disease eligible for treatment. Questions may need rephrasing.*
- *According to availability.*
- *In regard to: When a biopsy is not feasible or when cytology does not provide enough material, ctDNA can be used for diagnosis. 1. the chance to find ctDNA when a biopsy is not feasible is extremely low 2. the clinical situation and biopsy determine what the next step is, the role of a ctDNA test has not been confirmed as a decision tool as yet.*
- *I am conceptually in agreement, but molecular profiling is still not available in many centers.*
- *Not always implications.*
- *Molecular profiling of CCA should be done in any case after a histological diagnosis.*

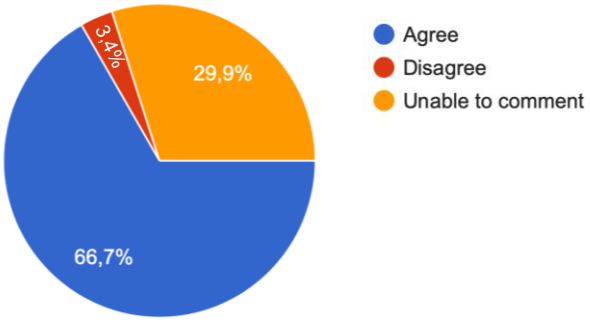
IV. TUMOUR BIOLOGY

20) *To meet the anabolic demands, malignant cells and cellular components of the microenvironment tend to rewire their metabolic pathways. Although different types of malignant cells share this phenomenon, there is a great intracellular variability of these metabolic patterns.*

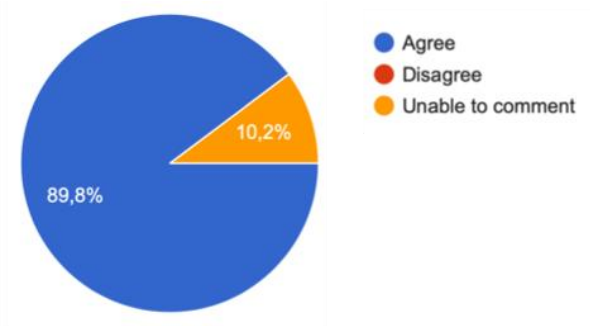
- Agree
- Disagree
- Unable to comment



21) *Developing compounds that target key players of mitochondrial pathways may be promising in CCA.*
    - Agree
    - Disagree
    - Unable to comment

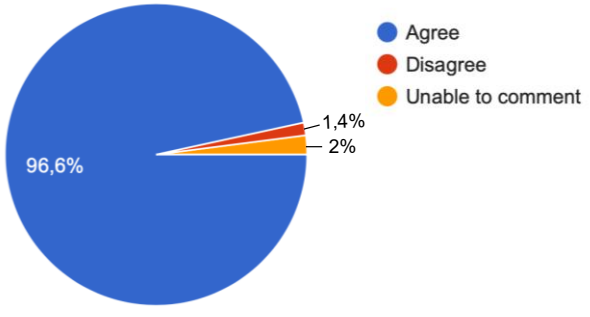


22) *CCAs are highly desmoplastic and hypovascularized tumours. Stroma content and composition affect the progression, evolution and response to systemic therapies.*
    - Agree
    - Disagree
    - Unable to comment

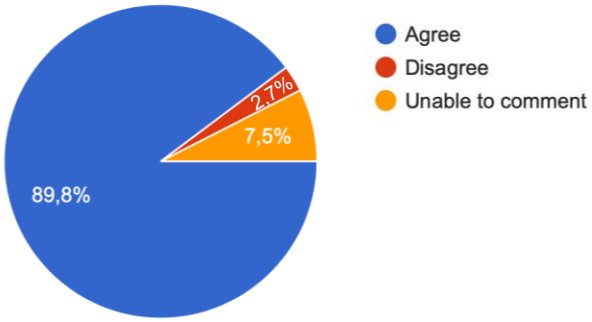


V. BIOMARKERS

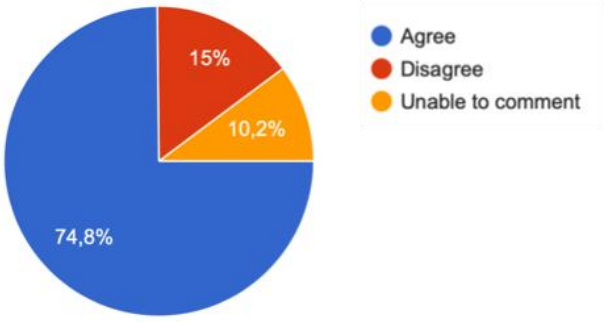
23) *For their clinical implementation, biomarkers should be prospectively validated for the intended purpose (e.g. diagnostic, prognostic, predictive, or pharmacodynamic) in international cohorts including individuals with different risk factors and ethnicities, and compared to appropriate control groups.*
    - Agree
    - Disagree
    - Unable to comment



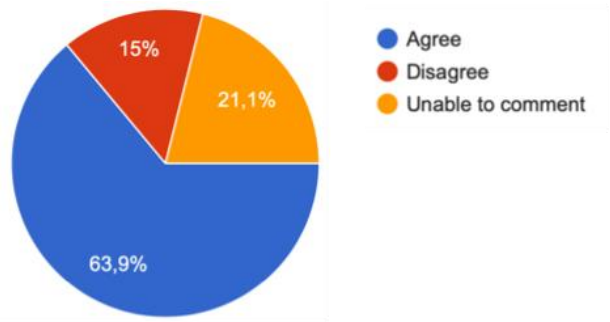
24) *Serum CA19-9 and CEA levels are not accurate biomarkers particularly for the detection of small CCA lesions (early tumor stages).*
    - Agree
    - Disagree
    - Unable to comment



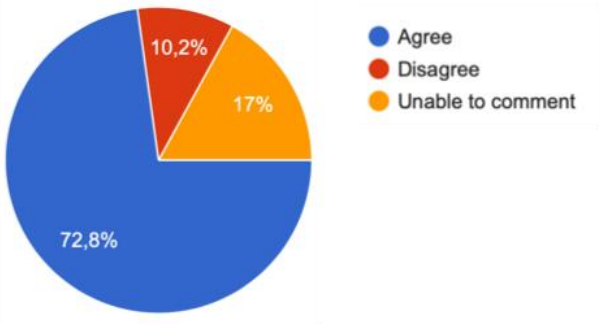
25) *Serum CA19-9 and CEA levels should be used as comparators for the development of novel biomarkers for the early diagnosis of CCA*
    - Agree
    - Disagree
    - Unable to comment



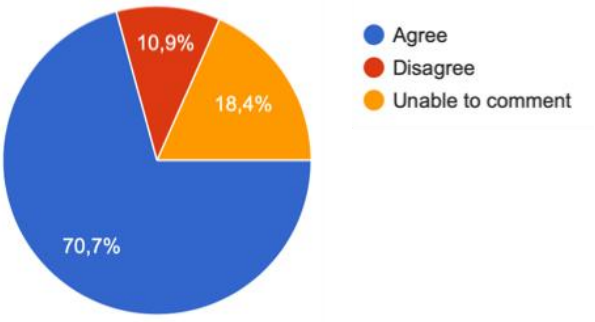
26) *Serum CA19-9 levels (in known secretors and in the absence of biliary obstruction) have independent prognostic value on overall survival for patients and should be balanced between groups in clinical trial design.*
    - Agree
    - Disagree
    - Unable to comment



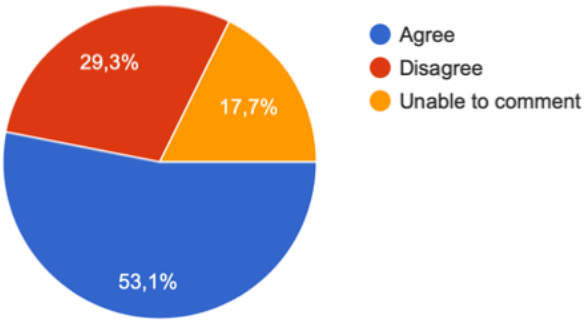
27) *Serum CA19-9 levels correlate with radiological response to systemic therapies and should be monitored clinically during treatment.*
    - Agree
    - Disagree
    - Unable to comment



28) *Serum AFP should be tested and monitored in cases of iCCA arising from liver cirrhosis*
    - Agree
    - Disagree
    - Unable to comment

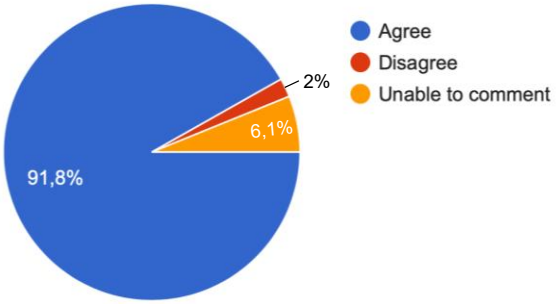


29) *There are biomarkers that support systemic therapy decision making.*
    - Agree
    - Disagree
    - Unable to comment

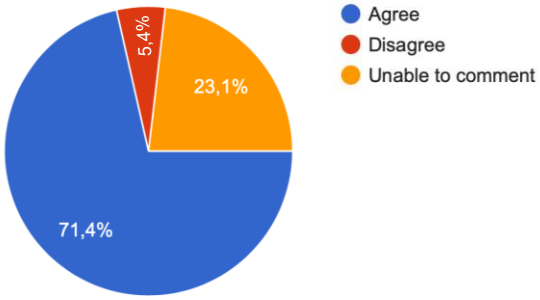


VI. TREATMENT

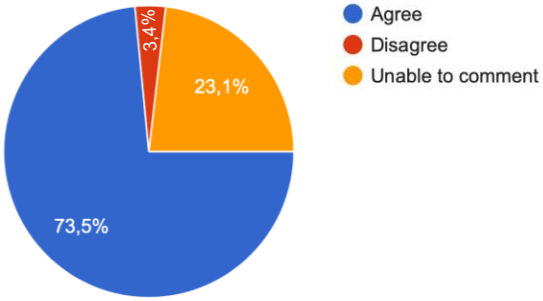
30) *Consensus on radiological criteria for resectability of CCA is needed.*
- Agree
- Disagree
- Unable to comment



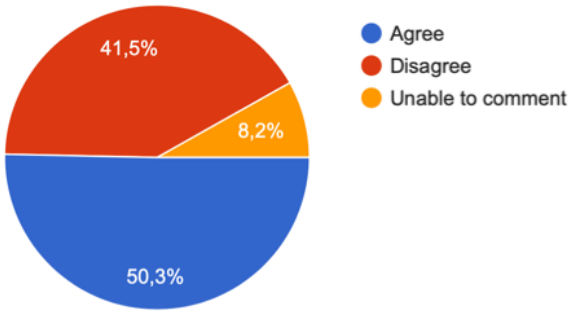
31) *In patients with a cirrhotic liver presenting an iCCA single tumour ≤2cm liver transplantation can be a therapeutic option.*
- Agree
- Disagree
- Unable to comment



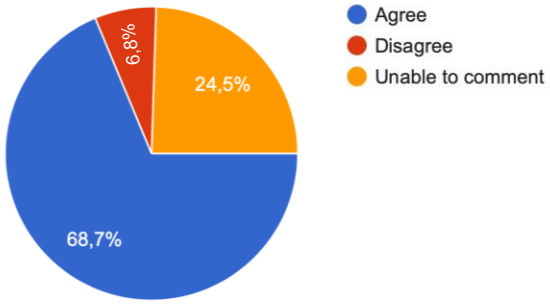
32) *Liver Transplantation for perihilar cholangiocarcinoma (pCCA) may be a therapeutic option in patients with unresectable pCCA, ≤3cm in radial size, and no extrahepatic disease or lymph node spread.*
- Agree
- Disagree
- Unable to comment



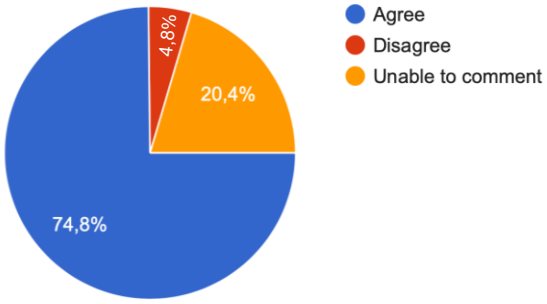
33) *In the era of precision medicine, chemotherapy is of benefit for all patients with advanced CCA.*
- Agree
- Disagree
- Unable to comment



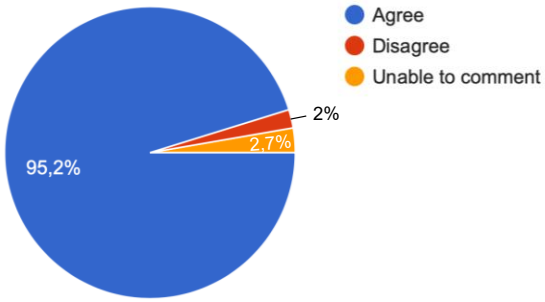
34) *PSC and PBC are immune-mediated liver diseases; the triple combination of gemcitabine, cisplatin and immunotherapy in first-line should be also considered in patients with CCA arising in these backgrounds considering the risk-benefit.*
- Agree
- Disagree
- Unable to comment



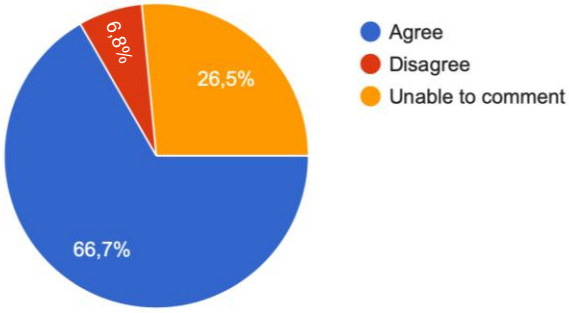
35) *FOLFOX is a chemotherapy regimen to be considered in patients who progressed to first line treatment, in absence of druggable alterations, after weighing up the potential risks and benefits.*
- Agree
- Disagree
- Unable to comment



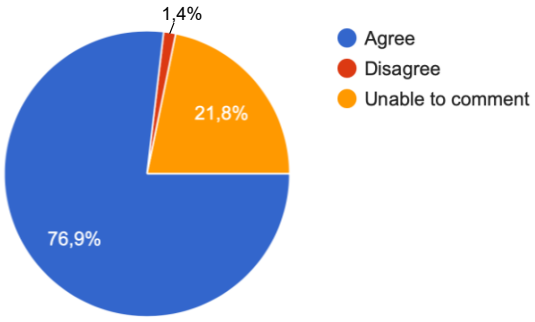
36) *Understanding the effect of chemotherapy and immunotherapy in CCAs with specific actionable genetic alterations may impact clinical decisions.*
    - Agree
    - Disagree
    - Unable to comment



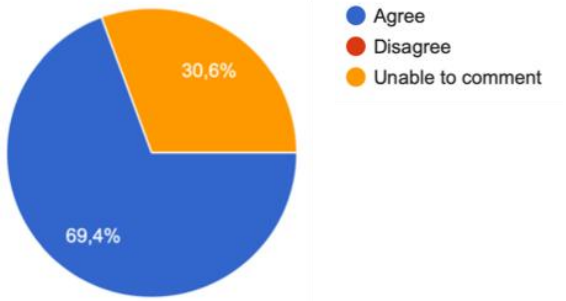
37) *dMMR/MSI-H is a good predictive biomarker of response to immunotherapy in CCA.*
    - Agree
    - Disagree
    - Unable to comment



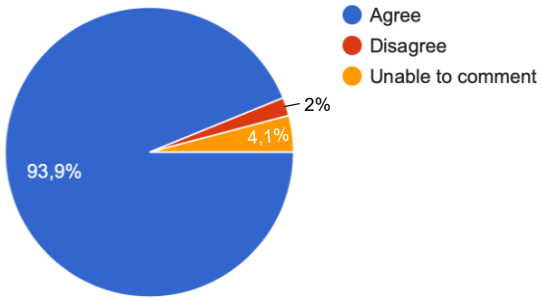
38) *HER2 overexpression and/or amplification is a good predictive biomarker of response to anti-HER2 regimens.*
    - Agree
    - Disagree
    - Unable to comment



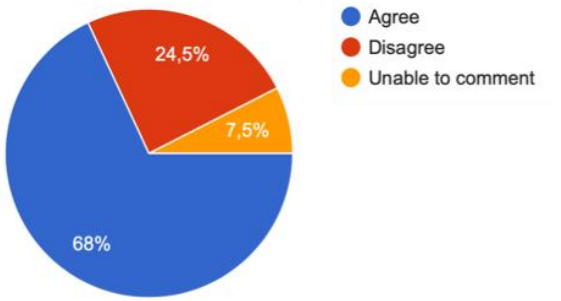
39) *Patients with CCA and BRAF^{V600E} mutation previously treated with ≥1 line of systemic therapy should be considered for treatment with dabrafenib-trametinib, when available.*
    - Agree
    - Disagree
    - Unable to comment



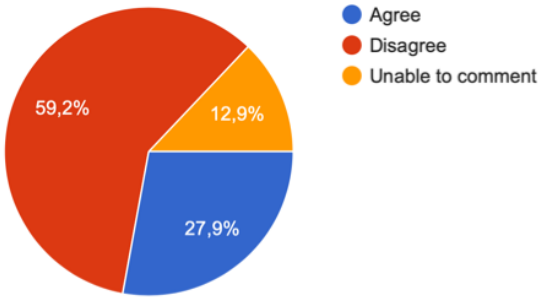
40) *Molecular testing of advanced biliary tract cancer should be panel-based and broader than for known actionable alterations for which therapies are already available in order to be able to consider new targeted therapies in development in the setting of clinical trials*
    - Agree
    - Disagree
    - Unable to comment



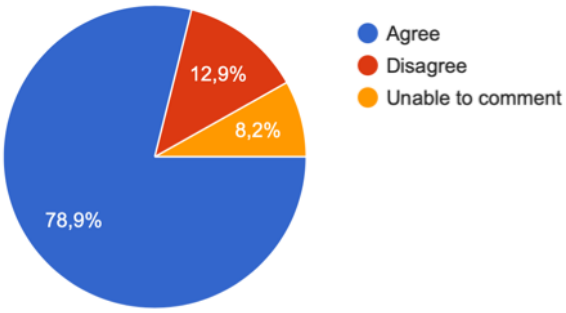
41) *Progression free survival (PFS) is an appropriate surrogate marker of treatment response in clinical trials with patients with CCA.*
    - Agree
    - Disagree
    - Unable to comment



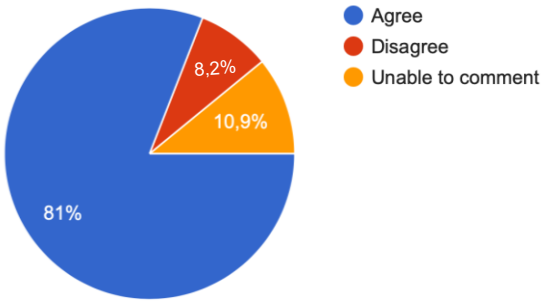
42) *Progression free survival (PFS) should be sufficient as a primary end-point in clinical trials with patients with CCA.*
- Agree
- Disagree
- Unable to comment



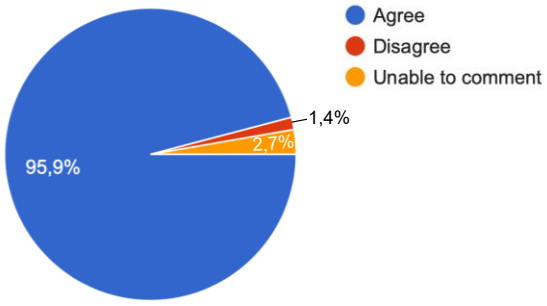
43) *Overall survival (OS) should be the primary end-point in clinical trials with patients with CCA.*
- Agree
- Disagree
- Unable to comment



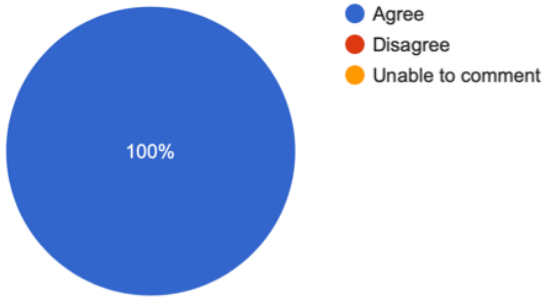
44) *Single-arm clinical trials with targeted therapies could benefit from data of the natural course of matched patients obtained from international clinical registries for regulatory approval.*
- Agree
- Disagree
- Unable to comment



45) *Treatment recommendations for patients with CCA should be based on discussions in multidisciplinary tumour boards.*
    - Agree
    - Disagree
    - Unable to comment

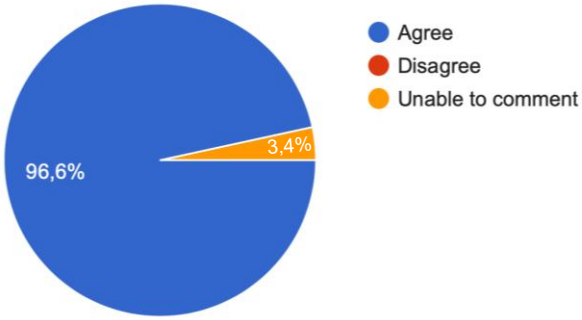


46) *Collection of biological samples should be pursued within clinical trials and clinical practice to improve understanding of the disease, the impact of therapies and ultimately improve patient outcomes.*
    - Agree
    - Disagree
    - Unable to comment

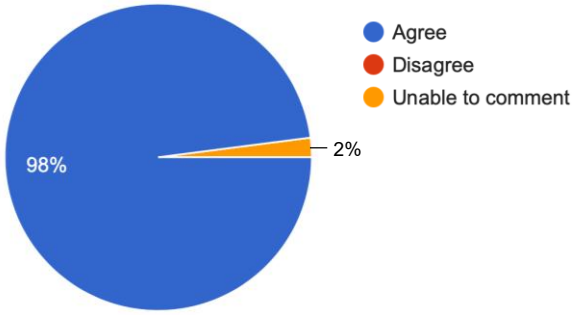


VII. SUPPORTIVE CARE

47) *Upon CCA diagnosis, psychological support should be considered.*
    - Agree
    - Disagree
    - Unable to comment

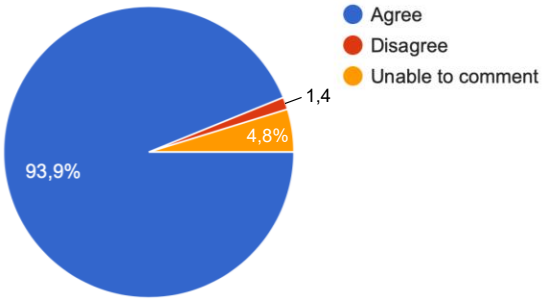


48) *Upon CCA diagnosis, dietary and nutrition counselling should be recommended.*
- Agree
- Disagree
- Unable to comment

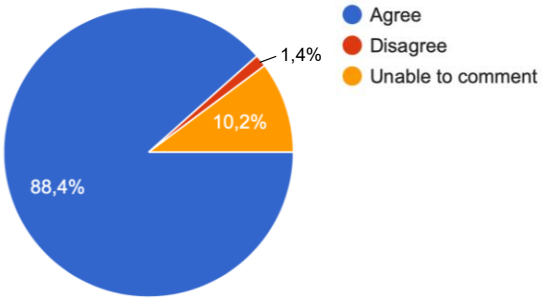


VIII. FUTURE RESEARCH

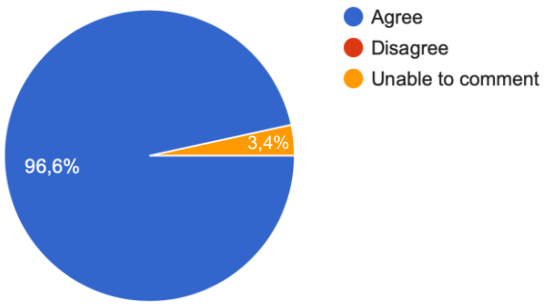
49) *Further research is needed to assess if patients-derived advanced 3D culture models (i.e., organoids, organ-on-a-chip, precision-cut liver slices, among others) can be used to tailor therapeutic approaches related to specific signalling pathways or altered processes.*
- Agree
- Disagree
- Unable to comment



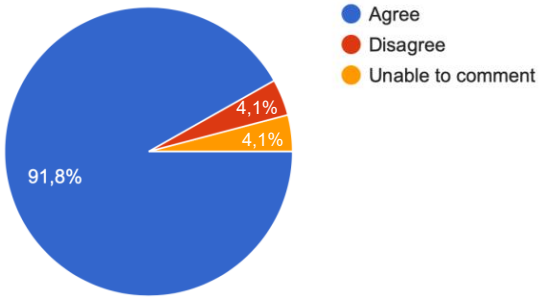
50) *Highly proliferative CCA cells rely on increased lipid and lipoprotein uptake and metabolization to support their growth. More research is needed to determine the clinical implications of these findings (i.e. diet advice; therapeutic manipulation).*
- Agree
- Disagree
- Unable to comment



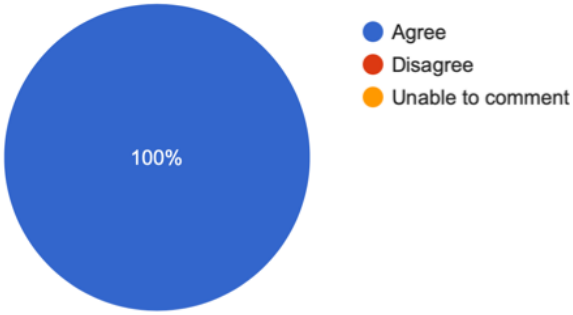
51) *Strategies aiming to modulate the CCA tumour immune microenvironment (TIME) deserve further investigations to expand therapeutic targets.*
    - Agree
    - Disagree
    - Unable to comment



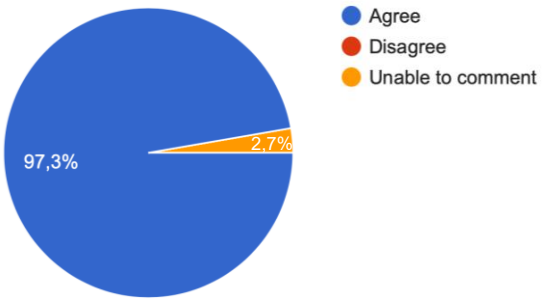
52) *CCA classes identified by molecular and immune characterization have been proposed to be clinically relevant in terms of patient outcome. These molecular classifications should be clinically investigated in prospective trials.*
    - Agree
    - Disagree
    - Unable to comment



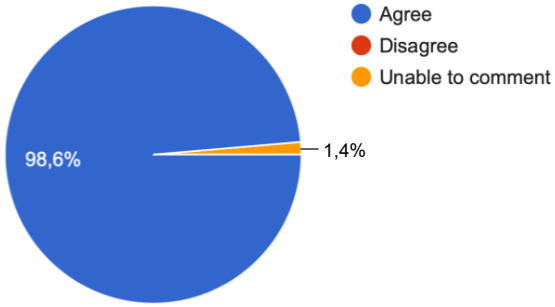
53) *Further research in biomarker for systemic therapy response is needed.*
    - Agree
    - Disagree
    - Unable to comment



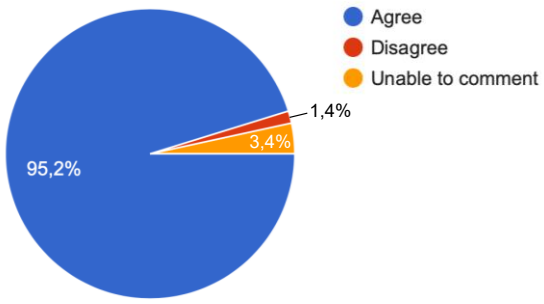
54) *Clinical investigation of the role of neoadjuvant systemic treatment in non-metastatic CCA is needed.*
    - Agree
    - Disagree
    - Unable to comment



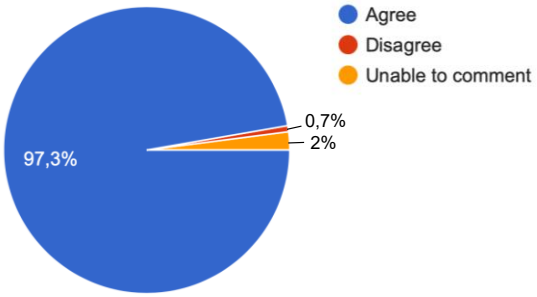
55) *Further clinical investigation is needed to identify the role of local therapy in CCA and their appropriate combination with systemic treatments.*
    - Agree
    - Disagree
    - Unable to comment



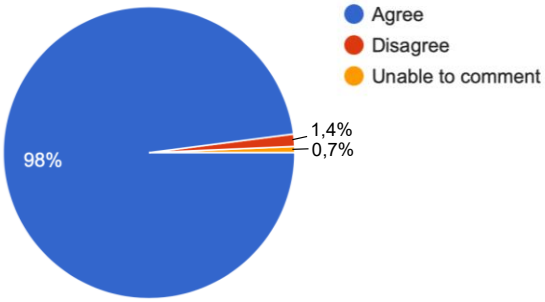
56) *The impact of systemic treatment according to the location of the CCA should be assessed in the future.*
    - Agree
    - Disagree
    - Unable to comment



57) *Investigation of the role of targeted therapies in first line is relevant in patients with advanced (unresectable or metastatic) disease.*
    - Agree
    - Disagree
    - Unable to comment



58) *The role of liquid biopsy to monitor tumour evolution during treatment should be investigated in prospective studies.*
    - Agree
    - Disagree
    - Unable to comment



59) *Predictive biomarkers of treatment response to immunotherapy are highly needed.*
    - Agree
    - Disagree
    - Unable to comment