REVIEW ARTICLE

The impact of imaging on the surgical management of biliary cystadenomas and cystadenocarcinomas; a systematic review

Anne J. Klompenhouwer[1,1], David W.G. ten Cate[1,1], Francois E.J.A. Willemssen[2], Wichor M. Bramer[3], Michael Doukas[4], Robert A. de Man[5] & Jan N.M. Ijzermans[1]

[1]Erasmus MC, University Medical Center Rotterdam, Department of Surgery, [2]Erasmus MC, University Medical Center Rotterdam, Department of Radiology, [3]Erasmus MC, University Medical Center Rotterdam, Medical Library, [4]Erasmus MC, University Medical Center Rotterdam, Department of Pathology, and [5]Erasmus MC, University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Rotterdam, the Netherlands

Abstract

Background: Biliary Cystadenomas (BCA) are considered to be benign but may transform to Biliary Cystadenocarcinomas (BCAC). The aim of this systematic review was to assess the diagnostic work-up and necessity of complete surgical resection.

Method: A systematic literature search was performed in Embase.com, Medline (Ovid), Cochrane Central, Web-of-Science and Google Scholar. Articles reporting on diagnostic work-up or outcome of various treatment strategies were included.

Results: Fifty-one articles with 1218 patients were included: 971 with BCA and 247 with BCAC. Patients with BCA were more often female (91% vs 63.8%, $p < 0.001$). On radiologic imaging BCAC more often had calcifications ($p = 0.008$), mural nodules ($p < 0.001$) and wall enhancement ($p < 0.001$). Reported treatment strategies were resection, enucleation, or fenestration/marsupialization. Recurrence was reported in 5.4% after resection for BCA and 4.8% after resection for BCAC. Recurrence after fenestration/marsupialization varied from 81.6% to 100% for both BCA as BCAC. Mortality rate was 0 in patients with BCA and 24% in BCAC.

Conclusion: Due to the difficulty in accurately diagnosing these biliary cystic lesions and the availability of different surgical approaches, patients with suspected BCA or BCAC should be treated in a center specialized in liver surgery with state-of-the-art imaging and all surgical techniques to prevent mismanagement of this rare disease.

Received 17 January 2019; accepted 12 April 2019

Correspondence

J.N.M. Ijzermans; A.J. Klompenhouwer, Erasmus MC, University Medical Center Rotterdam, Department of Surgery, Rotterdam, the Netherlands. E-mails: j.ijzermans@erasmusmc.nl (J.N.M. Ijzermans); a.klompenhouwer@erasmusmc.nl (A.J. Klompenhouwer)

Introduction

Biliary Cystadenomas (BCA) and biliary cystadenocarcinomas (BCAC), are rare complex cystic tumors that may arise within the biliary system of the liver or in the extrahepatic bile ducts including gallbladder (90 vs 10%, respectively).[1] Liver cysts are the most frequent liver lesions with an estimated frequency of 20% of the general population and less than 5% of all liver cysts are considered BCA.[2] BCA are considered to be benign, however literature suggests that up to 20% can transform to BCAC.[2–4] Due to the rarity of the disease, pathogenesis is still unclear and predictors of malignant behavior are yet to be discovered.

BCA almost exclusively occur in middle aged women[3,5,6] while BCAC appear to be more evenly distributed between men and women.[7] The average age at which BCA is diagnosed lies around 45 years compared to 55 for BCAC.[3,8] Patients with BCA most

[1] Shared first authorship.

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

often present with abdominal pain or discomfort[9] but jaundice,[10–12] nausea and vomiting have also been reported.[13]

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are most commonly used in diagnosing BCA. Using CT-scanning only, it may be difficult to differentiate simple cysts with septations from BCA. Several studies indicate that with Contrast Enhanced UltraSonography (CEUS) imaging features of cystic and cystic like focal liver lesions can be identified that may be helpful in differentiating simple cysts with septations from BCA (C), whereas conventional UltraSonography is not reliable to make this differentiation.[14,15] Biomarkers such as CA19-9, CA12-5, CEA and AFP may be elevated in both BCA and BCAC.[16–20]

For a definite BCA diagnosis histologic examination is required, showing multilocular, cystic lesions with thin walls. BCA are lined by cuboidal to columnar epithelium and have dense cellular ovarian-like stromata (OS).[3] In 2010 the World Health Organization (WHO) established that OS is a requirement for diagnosis and that it should be considered to rename the lesions to Mucinous Cystic Neoplasms (MCN).[21] The cysts are septated and contain mucinous or serous fluid.[6] They have been reported to appear more often in the left hemiliver[10,22] and range in size from 1 cm to 40 cm.[9]

BCA are considered to be slow growing tumors.[6,23] Because of the possible malignant transformation, additional diagnostic tests like biopsy or definitive treatment by resection is recommended. It is still open for discussion which treatment modality is preferable in case of BCA and options may vary from surgical resection to fenestration, marsupialization and drainage.[9,18,24,25] Literature suggests resection of every suspected BCA is currently recommended,[3,26,27] because other treatment options are correlated with a high recurrence rate.[16] However, as not every BCA will transform to BCAC, treatment of these lesions by complex surgical procedures with their associated complications should be carefully considered, against the possibility the resected lesion may be benign.[16]

To date, there is no clear evidence-based consensus on the optimal BCA (C) treatment strategy. As the disease is rare and the articles published are limited and potentially biased by expert opinions, this systematic review will assess the diagnostic work-up and necessity of complete surgical resection and aims to recommend on a justified management strategy.

Methods

This systematic review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline.[28]

Literature search

With the help of a clinical librarian (WMB) a systematic literature search was conducted using various synonyms for 'cystadenoma', 'mucinous cystic neoplasm' or 'cystadenocarcinoma' (appendix A). The search was conducted in Embase.com, Medline (Ovid), Cochrane Central, Web-of-Science and Google Scholar. The date last searched was November 22nd 2017.

Study selection

Two independent reviewers (AJK & DWGtC) evaluated the articles and screened title and abstract of all deduplicated articles. Articles were included if they reported on randomized controlled trials, case–control studies, cohort studies and case series ($n \geq 5$). The articles had to include patients diagnosed with BCA (C) and had to report on diagnostic work-up or outcome of various management strategies. Only articles written in English were included. If the inclusion criteria were met, full articles were reviewed. Disagreement was resolved by discussion.

Articles were excluded if they described tumors other than intrahepatic BCA. Reviews, animal studies, cadaver studies, case reports ($n < 5$), surveys, editorials, commentaries, conference abstracts and letters were also excluded. Additionally, articles that did not report on enrollment dates or enrollment centers were excluded in order to prevent reporting on overlapping data. When there was an overlap between different articles in study population, the article reporting the most complete data was chosen. Level of evidence was determined using Oxford Center for Evidence-based Medicine Levels of Evidence.[29]

Outcome measures

The primary outcomes were the reported BCA (C) associated mortality rates and recurrence rates after various treatment strategies. Patients who died due to BCA (C) unrelated disease were not included in mortality rate calculations. Secondary outcomes included a comparison of BCA vs BCAC based on patient characteristics and imaging characteristics. Data extraction was performed by AJK and DWG independently. Publication details, type of study, data on diagnostic work-up (biopsy, imaging [modality, diagnosis, characteristics], tumor markers [in serum and cystic fluid]), patient characteristics (sex, age at diagnosis, presentation), tumor characteristics (size, location), follow-up period, type of treatment (fenestration and marsupialization were categorized as one treatment group) and outcome (mortality and recurrence) were collected. Mortality was defined as death of disease or death of other cause.

Statistical analysis

Variables are presented as mean (SD) or median (range), according to the way they were reported in the original article. Differences between groups were investigated using Chi–Square test (IBM SPSS software version 21.0 Chicago, Illinois). Cumulative data were tabulated and presented as number with percentages.

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Results

The initial search yielded 6919 articles, of which 3455 remained after deduplication. Screening of title and abstract excluded 3316 articles, resulting in 139 articles for full text review. A final 51 articles were included in this systematic review. Article selection is depicted in Fig. 1.

Patient characteristics

The included articles are presented in Table 1. All studies included were retrospective case series or cohort studies (level of evidence 4). Table 2 describes the included patients in this study. A total of 1218 patients were included, of which 1022 (85.3%) were female. A total of 971 (79.7%) patients were diagnosed with BCA and 247 (20.3%) with BCAC.

A comparison between patients with BCA and BCAC showed a significantly higher proportion of female patients with BCA ($p < 0.001$). The age of patients with BCA ranged from 38 to 62 years and for BCAC from 49.4 to 77 years. No significant difference was found for tumor location or symptoms as well as liver function tests, including ALT, AST, Total Bilirubin and Alkaline Phosphatase levels. Analysis of tumor markers in serum and cystic fluid showed that patients with BCAC more often have elevated CA19-9 ($p = 0.041$) and CEA in serum ($p = 0.024$). No significant differences were found for CA12-5 and AFP in serum nor for any tumor markers in cystic fluid.

Diagnostics

All included patients had histologically confirmed BCA (C). In 678 patients (55.7%) CT was used and in 142 patients (11.7%) diagnosis was based on MRI. Contrast-Enhanced Ultrasound (CEUS) was performed in 41 patients (3.4%). In 79 patients (6.4%) both CT and MRI was used in the diagnostic work-up.

The imaging characteristics are described in Table 3. Calcifications were more often reported in patients with BCAC (55 (13.3%) in BCA and 22 (24.4%) in BCAC, $p = 0.008$), as were wall enhancement (81 (26.6%) in BCA and 52 (69.9%) in BCAC, $p < 0.001$) and mural nodules (81 (17.2%) in BCA and 76 (73.8%) in BCAC, $p < 0.001$). No statistically significant differences were found for multiloculation, septation and biliary dilatation. Out of 1218 histologically confirmed BCA (C), the presence of OS was described in 44% of the cases. OS was reported in 389 (88.8%) BCA and 63 (67%) BCAC ($p < 0.001$).

Treatment and outcome

Information on treatment was given for 832 patients with BCA and 212 patients with BCAC.

Resection was the most reported treatment strategy (BCA 91.7% and BCAC 92.9%). Other reported strategies were: fenestration (BCA 4.4%, BCAC 0.9%), enucleation (BCA 3.5%, BCAC 4.7%), marsupialization (BCA 0.1%, BCAC 0), liver transplantation (BCA 0.2%, BCAC 0.5%), drainage (BCA 0%, BCAC 0.5%), chemotherapy (BCA 0%, BCAC: 0.9%) and conservative treatment (BCA 0, BCAC 0.5%).

BCA recurrence occurred in 5.4% after resection, 3.3% after enucleation and in 81,6% after fenestration or marsupialization (Table 4). The reported recurrence rate for BCAC after resection was 4.8%, 9.1% after enucleation and 100% after fenestration or marsupialization. The BCA associated mortality rate was 0% (7/621 patients died, all causes unrelated to BCA). The BCAC associated mortality rate was 24.2% (42/172), four patients died as a result of BCAC unrelated disease. The difference in mortality between BCA and BCAC was statistically significant ($p < 0.001$).

Discussion

This systematic review included a total of 1218 patients extracted from 51 articles, 79.7% with BCA and 20.3% with BCAC. Although both BCA and BCAC occur predominantly in females, a significantly higher proportion of men was seen in the BCAC group. Median age of patients with BCAC appears to be higher than BCA (range 49–77 versus 38–62 years, respectively). It has been suggested that occurrence of BCA (C) is related to the embryonic gallbladder development and therefore lesions would be more often located in the left hemiliver.[9,10,22] However, in this study no statistically significant difference in tumor location between right and left hemiliver was found.

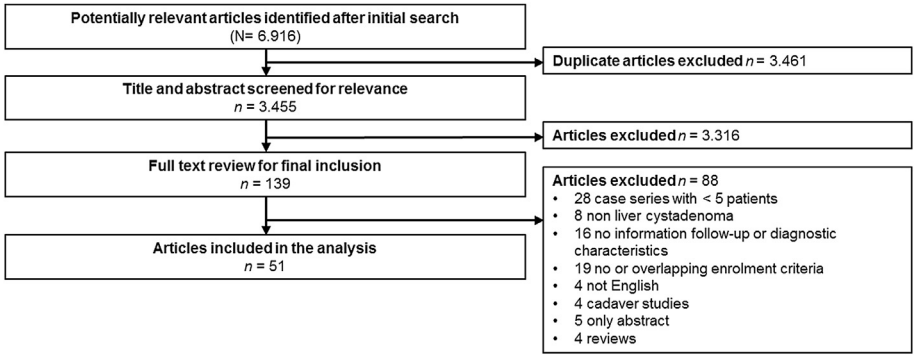

Figure 1 Flowchart inclusion

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Table 1 Overview of included studies

Reference	Year	Type of study (level of evidence)	No. Of patients	Mean/median age	Female: male	Mean/median tumor size (cm)	Treatment
1. Ahanatha et al.[39]	2012	Case series (4)	13	BCA: 46	11 : 2	–	Resection Enucleation
2. Al-Qahtani et al.[40]	2016	Case series (4)	11	BCA: 45.9	11 : 0	–	Resection Enucleation
3. Ammori et al.[41]	2002	Case series (4)	8	50[a]	5 : 3	12[a]	Resection Percutanous Drainage Conservative
4. Arnaoutakis et al.[16]	2015	Retrospective cohort (4)	248	BCA: 51.2 BCAC: 58,9	215 : 33	BCA: 10 BCAC: 10.5	Resection Fenestration Liver Transplantation
5. Buetow et al.[42]	1995	Case series (4)	34	BCA: 38 BCAC: 57	31 : 3	BCA: 12	Resection
6. Chen et al.[43]	2014	Case series (4)	39	53.7[a]	30 : 9	–	Resection Enucleation
7. Choi et al.[19]	2010	Retrospective cohort (4)	17	BCA: 57	17 : 0	BCAC: 10.1	Resection
8. Devaney et al.	1994	Case series (4)	70	BCA: 45 BCAC: 59	60 : 10	BCA: 15 BCAC: 12.3	Resection
9. Dong et al.[14]	2017	Case series (4)	23	BCA: 57 BCAC: 60	11 : 12	BCA: 4.8 BCAC: 6.9	–
10. Doussot et al.[32]	2015	Case series (4)	20	62[a]	17 : 3	9.9[a]	Resection
11. Emre et al.[24]	2011	Case series (4)	9	49[a]	9 : 0	–	Resection Enucleation
12. Fragulidis et al.[44]	2015	Case series (4)	10	BCA: 66 BCAC: 61	9 : 1	BCA: 9.9 BCAC: 13.5	Resection Enucleation
13. Gadzijev et al.[45]	1998	Case series (4)	6	BCA: 42.2 BCAC: 58	6 : 0	BCA: 10.8 BCAC: -	–
14. Hai et al.[46]	2003	Case series (4)	6	BCA: 56,3 BCAC: 59.6	4 : 2	BCA: 8 BCAC: 8.5	–
15. Hansman et al.[47]	2001	Case series (4)	8	–	–	–	Resection
16. Jae et al.[48]	2009	Case series (4)	10	BCA: 45.2 BCAC: 62	7 : 3	BCA: 8 BCAC: 9.6	Resection
17. Jwa et al.[17]	2017	Case series (4)	30	BCA: 60 BCAC: 68	27 : 3	–	Resection
18. Kim et al.[49]	2014	Case series (4)	15	BCA: 44	15 : 0	BCA: 8.7	Resection
19. Kim et al.[50]	2010	Case series (4)	12	56.3[a]	10 : 2	9.5[a]	–
20. Krige et al.[51]	2017	Case series (4)	16	BCA: 46	16 : 0	–	Resection
21. Labib et al.[20]	2017	Case series (4)	13	BCA: 46	13 : 0	BCA: 13.7	Resection
22. Lam et al.[52]	2008	Case series (4)	8	BCA: 45.7	8 : 0	–	–
23. Lee et al.[53]	2015	Case series (4)	21	BCA: 57 BCAC: 67.5	16 : 5	BCA: 8.5	–
24. Lewis et al.[26]	1988	Case series (4)	15	BCA: 41	13 : 2	BCA: 12.5	Resection
25. Li et al.[54]	2009	cohort study	13	44.4[a]	11 : 2	11.2[a]	Resection
26. Li et al.[55]	2013	Case series (4)	10	BCA: 45 BCAC: 51.3	8 : 2	–	Resection
27. Lim et al.[56]	2007	Retrospective cohort (4)	17	50[a]	15 : 2	8.9[a]	Resection
28. Lin et al.[33]	2009	Case series (4)	5	–	–	–	–
29. Martel et al.[57]	2013	Case series (4)	13	52.1[a]	12 : 1	12.4[a]	Resection Enucleation
30. Nakajima et al.[58]	1992	Case series (4)	7	BCAC: 55	5 : 2	BCAC: 11.8	Resection Enucleation
31. Pitchaimuthu et al.[59]	2015	Case series (4)	29	BCA: 62	28 : 1	–	–

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Table 1 (*continued*)

Reference	Year	Type of study (level of evidence)	No. Of patients	Mean/median age	Female: male	Mean/median tumor size (cm)	Treatment
32. Pojchamarnwiputh et al.[5]	2008	Retrospective cohort (4)	12	BCA: 40.6 BCAC: 51.3	10 : 2	BCA: 12 BCAC: 11.9	Resection Enucleation
33. Quigley et al.[37]	2017	Case series (4)	36	BCA: 50.4 BCAC: 61	36 : 0	BCA: 11.2 BCAC: 17.5	Resection
34. Ratti et al.[60]	2012	Case series (4)	12	BCA: 45	12 : 0	–	Resection
35. Regev et al.[22]	2001	Case series (4)	9	BCA: 60.5 BCAC: 77	7 : 2	BCA: 14.3 BCAC: 19	Resection
36. Sanchez et al.[27]	1991	Case series (4)	19	BCA: 42	15 : 4	BCA: 11	Resection Aspiration
37. Sang et al.[61]	2011	Case series (4)	33	BCA: 44.2 BCAC: 57	22 : 11	BCA: 13 BCAC: 8.3	Resection Enucleation Fenestration
38. Seo et al.[11]	2010	Retrospective cohort (4)	20	BCA: 55.2 BCAC: 56.8	17 : 3	BCA: 12.9 BCAC: 11	Resection
39. Song et al.[62]	2012	Retrospective cohort (4)	30	BCA: 51.6 BCAC: 49.3	22 : 8	BCA: 7.9 BCAC: 11.7	Resection
40. Teoh et al.[2]	2006	Case series (4)	7	BCA: 51.5 BCAC: 74	5 : 2	BCA: 8.6 BCAC: 14.4	Resection Enucleation
41. Thomas et al.[63]	2005	Case series (4)	19	BCA: 48.3	18 : 1	–	Resection Enucleation Fenestration
42. Treska et al.[64]	2016	Case series (4)	12	BCA: 57.7	12 : 0	–	Resection Enucleation
43. Vogt et al.[9]	2005	Case series (4)	22	BCA: 48 BCAC: 60	21 : 1	BCA: 12.5	Resection Enucleation
44. Wang et al.[10]	2012	Case series (4)	30	BCA: 44.2 BCAC: 56.9	23 : 7	BCA: 13 BCAC: 7.9	Resection
45. Wang et al.[65]	2014	Case series (4)	14	BCA: 48	11 : 3	BCA: 10.4	Resection
46. Wheeler et al.[6]	1985	Case series (4)	17	BCA: 41.7 BCAC: 58.8	17 : 0	–	Resection Drainage
47. Wu et al.[66]	2008	Case series (4)	7	BCA: 52	5 : 2	BCA: 10	Resection
48. Xu et al.[67]	2012	Case series (4)	13	BCA: 44 BCAC: 52	11 : 2	BCA: 8.2 BCAC: 8.6	Resection
49. Xu et al.[12]	2015	Retrospective cohort (4)	75	BCA: 45.4 BCAC: 57.5	58 : 17	BCA: 11.7 BCAC: 7.1	Resection Enucleation
50. Zen et al.[68]	2011	Retrospective cohort (4)	29	BCA: 45	29 : 0	BCA: 11	Resection
51. Zhang et al.[13]	2014	Case series (4)	46	BCA: 53.4 BCAC: 52	36 : 10	–	Resection

[a] Articles that combined BCA and BCAC in calculations.

This systematic review shows that liver function enzymes such as ALT, AST, total bilirubin and Alkaline Phosphatase, cannot be used to differentiate BCA from BCAC. Serum tumor markers CA19-9 and CEA are more often elevated in BCAC as compared to BCA. However, tumor markers within the normal range cannot rule out BCAC. No statistically significant differences were found for serum CA12-5 and AFP and for all tumor markers measured in cystic fluid. Even more, as tumor markers in cystic fluid can be elevated even in benign liver cysts,[30] these markers should not be used in the diagnostic work-up for BCA (C). Unfortunately, the exact level of the markers (times the upper limit of normal) were not reported.

On imaging, mural nodules, wall enhancement on contrast enhanced CT and calcifications occur significantly more often in BCAC as compared to BCA. Septations, multiloculation and biliary dilatation cannot be used reliably to differentiate BCA from BCAC. A recent study by Kovacs et al. performed in 25 patients with either complex hepatic cysts or BCA showed that the relationship between septations and the wall of the cystic lesion might be more predictive for a diagnosis than previously

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Table 2 Clinical characteristics and tumor markers

	BCA (N = 971) n (%)	BCAC (N = 247) n (%)	p-value
Gender			<0.001
Male	84 (9.3)	83 (36.2)	
Female	817 (90.7)	146 (63.8)	
No information	70	18	
Age (range)	38–62	49.4–77	
Presentation			0.492
Symptomatic	465 (74.6)	140 (82.4)	
Asymptomatic	158 (25.4)	30 (17.6)	
No information	348	77	
Tumor location			0.467
Left lobe	359 (55)	110 (59.8)	
Right lobe	207 (31.7)	54 (29.3)	
Bilobular	87 (13.3)	20 (10.9)	
No information	318	63	
ALT			0.291
Normal	124 (88.6)	49 (83.1)	
Elevated	16 (11.4)	10 (16.9)	
No information	831	188	
AST			0.888
Normal	124 (95.4)	56 (94.9)	
Elevated	6 (4.6)	3 (5.1)	
No information	841	188	
Total bilirubin			0.191
Normal	138 (89.6)	49 (83.1)	
Elevated	16 (10.4)	10 (16.9)	
No information	817	188	
Alkaline phosphatase			0.382
Normal	128 (94.8)	54 (91.5)	
Elevated	7 (5.2)	5 (8.5)	
No information	836	188	
CA19–9 – serum			**0.041**
Normal	257 (67.5)	62 (56.9)	
Elevated	124 (32.5)	47 (43.1)	
No information	590	138	
CEA – serum			**0.024**
Normal	196 (67.4)	22 (50)	
Elevated	95 (32.6)	22 (50)	
No information	680	203	
CA12–5 – serum			0.786
Normal	24 (82.8)	24 (80)	
Elevated	5 (17.2)	6 (20)	
No information	942	217	
AFP - serum			0.508
Normal	98 (99)	43 (100)	
Elevated	1 (1)	–	
No information	872	204	

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Table 2 (*continued*)

	BCA (N = 971) n (%)	BCAC (N = 247) n (%)	p-value
CA19–9 – cystic fluid			0.513
Normal	7 (17.9)	1 (33.3)	
Elevated	32 (82.1)	2 (66.7)	
No information	932	244	
CEA – cystic fluid			0.314
Normal	12 (34.3)	–	
Elevated	23 (65.7)	2 (100)	
No information	936	245	
CA12–5 – cystic fluid			–
Normal	–	–	
Elevated	13 (100)	–	
No information	958	247	

p-values < 0.05 are shown in bold.

reported imaging features.[31] Although the sample size in this study was small, the results are promising and should be explored further.

The disease related mortality rate for BCA was 0% as compared to 24.2% for patients with BCAC ($p < 0.001$). Unfortunately, no data are reported on a wait and see policy for BCA and therefore we cannot comment on the biological behavior and risk of transformation from BCA to BCAC. It would be of interest to study the natural course of these lesions in a well-defined prospective study. The reported recurrence rates

Table 3 Imaging characteristics

	BCA (N = 971) n (%)	BCAC (N = 247) n (%)	p-value
Multiloculation			0.551
Yes	359 (69.4)	71 (72.4)	
No	158 (30.6)	27 (27.6)	
No information	454	149	
Septation			0.385
Yes	328 (71.3)	69 (67)	
No	132 (28.7)	34 (33)	
No information	511	144	
Calcifications			**0.008**
Yes	55 (13.3)	22 (24.4)	
No	357 (86.7)	68 (75.6)	
No information	559	157	
Biliary dilatation			0.070
Yes	11 (18)	5 (41.7)	
No	50 (82)	7 (58.3)	
No information	910	235	
Mural nodules			**<0.001**
Yes	81 (17.2)	76 (73.8)	
No	391 (82.8)	27 (26.2)	
No information	499	144	
CEUS wall enhancement			**<0.001**
Yes	81 (26.6)	51 (69.9)	
No	224 (73.4)	22 (30.1)	
No information	666	174	

p-values < 0.05 are shown in bold.

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Table 4 Recurrence after treatment

BCA	
Resection (N = 763)	46 (5.4)
Enucleation (N = 37)	1 (3.3)
Fenestration or marsupialization (N = 38)	31 (81.6)
BCAC	
Resection (N = 197)	10 (4.8)
Enucleation (N = 10)	1 (9.1)
Fenestration or marsupialization (N = 2)	2 (100)

of different treatment strategies show a low recurrence after resection (5.4%) or enucleation (3.3%) and high recurrence rates after fenestration or marsupialization (81.6%). Unfortunately, data on the pre-operative diagnosis and the radicality of resection was lacking from the included articles. If the recurrence after resection were all non-radical resections the reason for recurrence may rather be the (inaccurate) treatment and not the disease.

This systematic review investigated BCA and BCAC, and did not look at the differentiation between complex liver cysts and BCA (C). In literature, we found that CT, MRI and ultrasound combined provide a high sensitivity (87.5–100%) for the differentiation of simple liver cysts from BCA (C),[32] but a poor specificity (43.1–53.4%). Another recently introduced imaging technique that might be used is CEUS, providing a sensitivity of 81.3–93.8% and specificity of 47.1–88.2%.[33] As all imaging modalities provide a poor specificity, future research should focus on ways to improve the diagnostic work-up, for example by combining CT and MRI with CEUS. A new approach to differentiate simple liver cysts from BCA (C) relies on measurement of intracystic tumor marker TAG-72, thus identifying BCA and BCAC.[34] The results of this study are promising and should be explored further.

Complications after surgery were underreported in the included articles. As BCA is essentially a benign disease and liver resections may have a complication rate of up to 20%,[35,36] perhaps resection of BCA should not be performed in all cases. In particular, lesions located nearby larger vessels might be at risk for complications due to surgery and decision-making should include the anatomical characteristics. It has been suggested that frozen section mid surgery could be performed to distinguish simple cysts from BCA and BCAC and avoid unnecessary resection.[32] In a study by Doussot et al. frozen section was performed in 36 patients with either simple cysts or BCA. They found a concordance between frozen section and final histopathological examination of resection specimen in all cases. This suggests that frozen section is a reliable way to distinguish simple cysts from BCA. However, a study performed by Quigley et al. found that to prove OS in the lesion, extensive pathological examination is required.[37] A selected part of the lesion as is taken for frozen section may not be representative for the lesion as a whole. Additionally, in the process of malignant transformation from BCA to BCAC, a biopsy is unlikely to be representative for the lesion as a whole as a biopsy is usually performed in the part that is easily accessible and not in the most suspect part of a liver lesion. Given the current uncertainty in differentiating BCA from BCAC and the high recurrence rates after fenestration and marsupialization, surgical resection should be the performed in all patients with suspected BCA (C). When BCAC is suspected, fenestration and marsupialization should never be performed.

The main limitation of this study lies in the histopathologic diagnostic criteria for BCA (C). These criteria changed in 2010 when the WHO established that BCA should be called Mucinous Cystic Neoplasms (MCN) and that the presence of OS is a requirement for MCN diagnosis.[21] To this day, OS is not widely applied and literature is highly conflicted on the definition of BCA (C) vs MCN.[38] One study reports that invasive carcinomas are uncommon in true MCN with OS,[37] while another states that OS positive MCN have a worse survival than patients with OS negative lesions.[16] In this systematic review, in over half of the patients (56%) information on stromal characteristics and especially the presence of OS was missing. Additionally, in the

Table 5 Summary of the main implications in the management of BCA (C)

Clinical characteristics	**BCA have a female predominance while BCAC occur are more evenly distributed between males and females. Patients with BCAC appear to be older.**
Tumor markers	Elevated serum tumor markers (CA19.9 and CEA) are suggestive for BCAC. However, tumor markers within the normal range cannot rule out BCAC.
Imaging	On imaging, calcifications, mural nodules and wall enhancement are more often reported in BCAC. The combination of CT, MRI and CEUS might improve the diagnostic work-up; this should be studied further.
Biopsy	Biopsy cannot be used to differentiate BCA from BCAC, as it is unlikely to be representative for the lesion as a whole.
Treatment	Radical resection should be performed in both BCA as BCAC, as fenestration or marsupialization have high recurrence rates. Fenestration or marsupialization should never be used for BCAC.
General conclusion	Patients with suspected BCA (C) should be treated in a center specialized in liver surgery with the availability of state-of-the-art imaging as well as surgical techniques to prevent mismanagement of this rare disease.

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

majority of included articles the presence of OS was only reported as frequency in the study population and not linked to patient characteristics or outcomes of individual patients, making it impossible for us to make a reliable statement about the association between OS and outcome. The second limitation of this systematic review is the fact that all included articles were retrospective cohort studies or case series (level of evidence 4[29]) resulting in missing data and bias. To the best of our knowledge, no prospective cohorts or randomized controlled trials have been published on this subject.

Conclusion

This systematic review shows that present data don't support a role for tumor markers in cystic fluid in differentiating BCA from BCAC. Radiologic imaging such as CT and MRI, but also CEUS, may help in differentiating BCA from BCAC, but their specificity is poor. A non-directed biopsy cannot be used to differentiate BCA from BCAC, as it is unlikely to be representative for the lesion as a whole. In case of suspected BCA (C), radical resection should be performed. Due to the variety in clinical symptoms, the difficulty in rightfully diagnosing BCA (C) and, in BCA, possible complications after resection of a benign neoplasm, patients with suspected BCA or BCAC should be treated in a center specialized in liver surgery with the availability of state-of-the-art imaging as well as surgical techniques to prevent mismanagement of this rare disease. A summary of the main implications for the management of BCA(C) is given in Table 5.

Grant support

Not applicable.

Disclosures

None of the authors have anything to disclose.

Writing assistance

Not applicable.

Author contributions

Study design: AJK, DWGtC, RAdM, JNMI.
Literature search: WMB.
Data collection: AJK, DWGtC
Data analysis and interpretation: AJK, DWGtC, FEJAW, WMB, MD, RAdM, JNMI.
Drafting of the manuscript: AJK, DWGtC, RAdM, JNMI.
Critical revision of the manuscript: AJK, DWGtC, FEJAW, WMB, MD, RAdM, JNMI.

Conflicts of interest

None declared.

References

1. Davies W, Chow M, Nagorney D. (1995) Extrahepatic biliary cystadenomas and cystadenocarcinoma: report of seven cases and review of the literature. *Ann Surg* 222:619–625.
2. Teoh AYB, Ng SSM, Lee KF, Lai PBS. (2006) Biliary cystadenoma and other complicated cystic lesions of the liver: diagnostic and therapeutic challenges. *World J Surg* 30:1560–1566.
3. Devaney K, Goodman ZD, Ishak KG. (1994) Hepatobiliary cystadenoma and cystadenocarcinoma: a light microscopic and immunohistochemical study of 70 patients. *Am J Surg Pathol* 18:1078–1091.
4. Erdogan D, Kloek J, Lamers WH, Offerhaus GJA, Busch ORC, Gouma DJ *et al*. (2010) Mucinous cystadenomas in liver: management and origin. *Dig Surg* 27:19–23.
5. Pojchamarnwiputh S, Na Chiangmai W, Chotirosniramit A, Lertprasertsuke N. (2008) Computed tomography of biliary cystadenoma and biliary cystadenocarcinoma. *Singap Med J* 49:392–396.
6. Wheeler DA, Edmondson HA. (1985) Cystadenoma with mesenchymal stroma (CMS) in the liver and bile ducts. A clinicopathologic study of 17 cases, 4 with malignant change. *Cancer* 56:1434–1445.
7. Ishak KG, Willis GW, Cummins SD, Bullock AA. (1977) Biliary cystadenoma and cystadenocarcinoma. Report of 14 cases and review of the literature. *Cancer* 39:322–338.
8. Läuffer JM, Baer HU, Maurer CA, Stoupis C, Zimmerman A, Büchler MW. (1998) Biliary cystadenocarcinoma of the liver: the need for complete resection. *Eur J Cancer* 34:1845–1851.
9. Vogt DP, Henderson JM, Chmielewski E. (2005) Cystadenoma and cystadenocarcinoma of the liver: a single center experience. *J Am Coll Surg* 200:727–733.
10. Wang C, Miao R, Liu H, Du X, Liu L, Lu X *et al*. (2012) Intrahepatic biliary cystadenoma and cystadenocarcinoma: an experience of 30 cases. *Dig Liver Dis* 44:426–431.
11. Seo JK, Kim SH, Lee SH, Park JK, Woo SM, Jeong JB *et al*. (2010) Appropriate diagnosis of biliary cystic tumors: comparison with atypical hepatic simple cysts. *Eur J Gastroenterol Hepatol* 22:989–996.
12. Xu MY, Shi XJ, Wan T, Liang YR, Wang HG, Zhang WZ *et al*. (2015) Clinicopathological characteristics and prognostic factors of intrahepatic biliary cystadenocarcinoma. *Chin Med J* 128:1177–1183.
13. Zhang FB, Zhang AM, Zhang ZB, Huang X, Wang XT, Dong JH. (2014) Preoperative differential diagnosis between intrahepatic biliary cystadenoma and cystadenocarcinoma: a single-center experience. *World J Gastroenterol* 20:12595–12601.
14. Dong Y, Wang WP, Mao F, Fan M, Ignee A, Serra C *et al*. (2017) Contrast enhanced ultrasound features of hepatic cystadenoma and hepatic cystadenocarcinoma. *Scand J Gastroenterol* 52:365–372.
15. Corvino A, Catalano O, Corvino F, Sandomenico F, Petrillo A. (2017) Diagnostic performance and confidence of contrast-enhanced ultrasound in the differential diagnosis of cystic and cysticlike liver lesions. *Am J Roentgenol* 209:W119–W127.
16. Arnaoutakis DJ, Kim Y, Pulitano C, Zaydfudim V, Squires MH, Kooby D *et al*. (2015) Management of biliary cystic tumors: a multi-institutional analysis of a rare liver tumor. *Ann Surg* 261:361–367.
17. Jwa EK, Hwang S. (2017) Clinicopathological features and post-resection outcomes of biliary cystadenoma and cystadenocarcinoma of the liver. *Ann Hepatobiliary Pancreat Surg* 21:107–113.
18. Koffron A, Rao S, Ferrario M, Abecassis M. (2004) Intrahepatic biliary cystadenoma: role of cyst fluid analysis and surgical management in the laparoscopic era. *Surgery* 136:926–936.

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

19. Choi HK, Lee JK, Lee KH, Lee KT, Rhee JC, Kim KH *et al*. (2010) Differential diagnosis for intrahepatic biliary cystadenoma and hepatic simple cyst: significance of cystic fluid analysis and radiologic findings. *J Clin Gastroenterol* 44:289–293.
20. Labib PL, Aroori S, Bowles M, Stell D, Briggs C. (2017) Differentiating simple hepatic cysts from mucinous cystic neoplasms: radiological features, cyst fluid tumour marker analysis and multidisciplinary team outcomes. *Dig Surg* 34:36–42.
21. Bosman F. (2010) *WHO classification of tumours of the digestive system*, 4th ed. Lyon: International Agency for Research on Cancer.
22. Regev A, Reddy KR, Berho M, Sleeman D, Levi JU, Livingstone AS *et al*. (2001) Large cystic lesions of the liver in adults: a 15-year experience in a tertiary center. *J Am Coll Surg* 193:36–45.
23. Woods GL. (1981) Biliary cystadenocarcinoma: case report of hepatic malignancy originating in benign cystadenoma. *Cancer* 47:2936–2940.
24. Emre A, Serin KR, Özden I, Tekant Y, Bilge O, Alper A *et al*. (2011) Intrahepatic biliary cystic neoplasms: surgical results of 9 patients and literature review. *World J Gastroenterol* 17:361–365.
25. Akwari OE, Tucker A, Seigler HF, Itani KMF. (1990) Hepatobiliary cystadenoma with mesenchymal stroma. *Ann Surg* 211:18–27.
26. Lewis WD, Jenkins RL, Rossi RL, Munson L, ReMine SG, Cady B *et al*. (1988) Surgical treatment of biliary cystadenoma. A report of 15 cases. *Arch Surg* 123:563–568.
27. Sanchez H, Gagner M, Rossi RL, Jenkins RL, Lewis WD, Munson JL *et al*. (1991) Surgical management of nonparasitic cystic liver disease. *Am J Surg* 161:113–119.
28. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M *et al*. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 4:1.
29. Medicine OCfE-B. (2011) *The Oxford levels of evidence 2*. OCEBM Levels of Evidence Working Group.
30. Iwase K, Takenaka H, Oshima S, Yagura A, Nishimura Y, Yoshidome K *et al*. (1992) Determination of tumor marker levels in cystic fluid of benign liver cysts. *Dig Dis Sci* 37:1648–1654.
31. Kovacs MD, Sheafor DH, Burchett PF, Picard MM, Hardie AD. (2018) Differentiating biliary cystadenomas from benign hepatic cysts: preliminary analysis of new predictive imaging features. *Clin Imaging* 49:44–47.
32. Doussot A, Gluskin J, Groot-Koerkamp B, Allen PJ, De Matteo RP, Shia J *et al*. (2015) The accuracy of pre-operative imaging in the management of hepatic cysts. *HPB* 17:889–895.
33. Lin MX, Xu HX, Lu MD, Xie XY, Chen LD, Xu ZF *et al*. (2009) Diagnostic performance of contrast-enhanced ultrasound for complex cystic focal liver lesions: blinded reader study. *Eur Radiol* 19:358–369.
34. Fuks D, Voitot H, Paradis V, Belghiti J, Vilgrain V, Farges O. (2014) Intracystic concentrations of tumour markers for the diagnosis of cystic liver lesions. *Br J Surg* 101:408–416.
35. Descottes B, Glineur D, Lachachi F, Surgical DV. (2003) *Laparoscopic liver resection of benign liver tumors*. Springer.
36. Dokmak S, Fteriche FS, Borscheid R, Cauchy F, Farges O, Belghiti J. (2013) Liver resections in the 21st century: we are far from zero mortality. *HPB* 15:908–915.
37. Quigley B, Reid MD, Pehlivanoglu B, Squires MH, 3rd, Maithel S, Xue Y *et al*. (2017) Hepatobiliary mucinous cystic neoplasms with ovarian type stroma (So-Called "hepatobiliary cystadenoma/cystadenocarcinoma"). In: *Clinicopathologic analysis of 36 cases illustrates rarity of carcinomatous change*.
38. Kishida N, Shinoda M, Masugi Y, Itano O, Fujii-Nishimura Y, Ueno A *et al*. (2014) Cystic tumor of the liver without ovarian-like stroma or bile duct communication: two case reports and a review of the literature. *World J Surg Oncol* 12:229.
39. Ahanatha Pillai S, Velayutham V, Perumal S, Ulagendra Perumal S, Lakshmanan A, Ramaswami S *et al*. (2012) Biliary cystadenomas: a case for complete resection. *HPB Surg* 2012:501705.
40. Al-Qahtani HH. (2016) Diagnostic uncertainty of hepatobiliary cystadenoma: report of 11 cases and review of the literature. *J Taibah Univ Med Sci* 11:19–25.
41. Ammori BJ, Jenkins BL, Lim PCM, Prasad KR, Pollard SG, Lodge JPA. (2002) Surgical strategy for cystic diseases of the liver in a western hepatobiliary center. *World J Surg* 26:462–469.
42. Buetow PC, Buck JL, Pantongrag-Brown L, Radiology PRR. (1995) *Biliary cystadenoma and cystadenocarcinoma: clinical-imaging-pathologic correlations with emphasis on the importance of ovarian stroma*. pubs RSNA org.
43. Chen YW, Li CH, Liu Z, Dong JH, Zhang WZ, Jiang K. (2014) Surgical management of biliary cystadenoma and cystadenocarcinoma of the liver. *Genet Mol Res* 13:6383–6390.
44. Fragulidis GP, Vezakis AI, Konstantinidis CG, Chondrogiannis KK, Primetis ES, Kondi-Pafiti A *et al*. (2015) Diagnostic and therapeutic challenges of intrahepatic biliary cystadenoma and cystadenocarcinoma: a report of 10 cases and review of the literature. *Int Surg* 100: 1212–1219.
45. Gadzijev EM, Pleskovic A, Stanisavljevic D, Ferlan-Marolt V, Trotovsek B. (1998) Hepatobiliary cystadenoma can protrude and grow into the bile ducts. *Hepato-Gastroenterology* 45:1446–1451.
46. Hai S, Hirohashi K, Uenishi T, Yamamoto T, Shuto T, Tanaka H *et al*. (2003) Surgical management of cystic hepatic neoplasms. *J Gastroenterol* 38:759–764.
47. Hansman MF, Ryan JA, Jr., Holmes IJH, Hogan S, Lee FT, Kramer D *et al*. (2001) Management and long-term follow-up of hepatic cysts. *Am J Surg* 181:404–410.
48. Jae HL, Kyeong GL, Hwon KP, Kwang SL. (2009) Biliary cystadenoma and cystadenocarcinoma of the liver: 10 Cases of a single center experience. *Hepato-Gastroenterology* 56:844–849.
49. Kim HJ, Yu ES, Byun JH, Hong SM, Kim KW, Lee JS *et al*. (2014) CT differentiation of mucin-producing cystic neoplasms of the liver from solitary bile duct cysts. *Am J Roentgenol* 202:83–91.
50. Kim JY, Kim SH, Eun HW, Lee MW, Lee JY, Han JK *et al*. (2010) Differentiation between biliary cystic neoplasms and simple cysts of the liver: accuracy of CT. *Am J Roentgenol* 195:1142–1148.
51. Krige JEJ, Jonas E, Beningfield SJ, Booth A, Kotze UK, Bernon M *et al*. (2017) Resection of benign liver tumours: an analysis of 62 consecutive cases treated in an academic referral centre. *S Afr J Surg* 55:27–34.
52. Lam MM, Swanson PE, Upton MP, Yeh MM. (2008) Ovarian-type stroma in hepatobiliary cystadenomas and pancreatic mucinous cystic neoplasms: an immunohistochemical study. *Am J Clin Pathol* 129: 211–218.
53. Lee CW, Tsai HI, Lin YS, Wu TH, Yu MC, Chen MF. (2015) Intrahepatic biliary mucinous cystic neoplasms: clinicoradiological characteristics and surgical results. *BMC Gastroenterol* 15.
54. Li T, Ji Y, Zhi X, Wang L, Yang X, Shi G *et al*. (2009) A comparison of hepatic mucinous cystic neoplasms with biliary intraductal papillary neoplasms. *Clin Gastroenterol Hepatol* 7:586–593.

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

55. Li X, Zhang JL, Wang YH, Song SW, Wang FS, Shi R *et al*. (2013) Hepatobiliary cystadenoma and cystadenocarcinoma: a single center experience. *Tumori* 99:261–265.

56. Lim JH, Jang KT, Rhim H, Kim YS, Lee KT, Choi SH. (2007) Biliary cystic intraductal papillary mucinous tumor and cystadenoma/cystadenocarcinoma: differentiation by CT. *Abdom Imag* 32:644–651.

57. Martel G, Alsharif J, Aubin JM, Marginean C, Mimeault R, Fairfull-Smith RJ *et al*. (2013) The management of hepatobiliary cystadenomas: lessons learned. *HPB* 15:617–622.

58. Nakajima T, Sugano I, Matsuzaki O, Nagao K, Kondo Y, Miyazaki M *et al*. (1992) Biliary cystadenocarcinoma of the liver: a clinicopathologic and histochemical evaluation of nine cases. *Cancer* 69: 2426–2432.

59. Pitchaimuthu M, Aidoo-Micah G, Coldham C, Sutcliffe R, Roberts JK, Muiesan P *et al*. (2015) Outcome following resection of biliary cystadenoma: a single centre experience and literature review. *Int J Hepatol* 2015.

60. Ratti FA, Ferla F, Paganelli M, Cipriani FA, Aldrighetti LA, Ferla G. (2012) Biliary cystadenoma: short-and long-term outcome after radical hepatic resection. *Updates Surg* 64:13–18.

61. Sang X, Sun Y, Mao Y, Yang Z, Lu X, Yang H *et al*. (2011) Hepatobiliary cystadenomas and cystadenocarcinomas: a report of 33 cases. *Liver Int* 31:1337–1344.

62. Song Y, Kang MJ, Jang JY, Lee KU, Suh KS, Kim SW. (2012) Clinical outcome and long term results after surgical treatment of biliary cystadenoma and cystadenocarcinoma. *Korean J Hepato-Biliary-Pancreatic Surg* 16:24–28.

63. Thomas KT, Welch D, Trueblood A, Sulur P, Wise P, Gorden DL *et al*. (2005) Effective treatment of biliary cystadenoma. *Ann Surg* 241: 769–775.

64. Treska V, Ferda J, Daum O, Liska V, Skalicky T, Bruha J. (2016) Intrahepatic biliary cystadenoma-diagnosis and treatment options. *Turk J Gastroenterol* 27:252–256.

65. Wang K, Kong F, Dong M, Zhou J, Li Y. (2014) Diagnosis and treatment of intrahepatic biliary cystadenoma: experience with 14 cases in a single center. *Med Oncol* 31:1–4.

66. Wu JM, Wu YM, Ho MC, Hu RH, Lee PH. (2008) Surgical treatment of biliary cystadenomas. *Int Surg* 93:373–376.

67. Xu HX, Lu MD, Liu LN, Zhang YF, Guo LH, Liu C *et al*. (2012) Imaging features of intrahepatic biliary cystadenoma and cystadenocarcinoma on B-mode and contrast-enhanced ultrasound. *Ultraschall Med* 33: E241–E249.

68. Zen Y, Pedica F, Patcha VR, Capelli P, Zamboni G, Casaril A *et al*. (2011) Mucinous cystic neoplasms of the liver: a clinicopathological study and comparison with intraductal papillary neoplasms of the bile duct. *Mod Pathol* 24:1079–1089.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.04.004.

© 2019 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.