

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2020 August 21; 26(31): 4567-4728



### REVIEW

- 4567** Current understanding of the metabolism of micronutrients in chronic alcoholic liver disease  
*Wu J, Meng QH*

### MINIREVIEWS

- 4579** COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract  
*Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, Viazis N, Liatsos C, Mantzaris GJ*

### ORIGINAL ARTICLE

#### Basic Study

- 4589** Feasibility and efficacy evaluation of metallic biliary stents eluting gemcitabine and cisplatin for extrahepatic cholangiocarcinoma  
*Xiao JB, Weng JY, Hu YY, Deng GL, Wan XJ*

#### Case Control Study

- 4607** Establishment of a pattern recognition metabolomics model for the diagnosis of hepatocellular carcinoma  
*Zhou PC, Sun LQ, Shao L, Yi LZ, Li N, Fan XG*

#### Retrospective Cohort Study

- 4624** Impact of interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer patients  
*Mei SW, Liu Z, Wei FZ, Chen JN, Wang ZJ, Shen HY, Li J, Zhao FQ, Pei W, Wang Z, Wang XS, Liu Q*

#### Retrospective Study

- 4639** Monocyte-to-lymphocyte ratio as a prognostic factor in peripheral whole blood samples of colorectal cancer patients  
*Jakubowska K, Koda M, Grudzińska M, Kańczuga-Koda L, Famulski W*
- 4656** Clinical and prognostic significance of CC chemokine receptor type 8 protein expression in gastrointestinal stromal tumors  
*Li HL, Wang LH, Hu YL, Feng Y, Li XH, Liu YF, Li P, Mao QS, Xue WJ*
- 4669** Initial experience of single-incision plus one port left-side approach totally laparoscopic distal gastrectomy with uncut Roux-en-Y reconstruction  
*Zhou W, Dong CZ, Zang YF, Xue Y, Zhou XG, Wang Y, Ding YL*
- 4680** Prognostic value of pretreatment contrast-enhanced computed tomography in esophageal neuroendocrine carcinoma: A multi-center follow-up study  
*Zhou Y, Hou P, Zha KJ, Wang F, Zhou K, He W, Gao JB*

- 4694** Clinical characteristics and risk factors for liver injury in COVID-19 patients in Wuhan

*Zhang H, Liao YS, Gong J, Liu J, Zhang H*

**Observational Study**

- 4703** Mucosal-associated invariant T cells in hepatitis B virus-related liver failure

*Xue H, Li H, Ju LL, Han XD, Cheng TC, Luo X, Chen L, Shao JG, She YJ, Bian ZL*

**SYSTEMATIC REVIEWS**

- 4718** Risk of malignancy in Caroli disease and syndrome: A systematic review

*Fahrner R, Dennler SG, Inderbitzin D*

**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, Dr. Tatsuo Kanda received an MD from the Niigata University School of Medicine (Japan) in 1991 and a PhD from the Graduate School of Medicine at Chiba University (Japan) in 1999. He then undertook post-doctoral training in the Departments of Pathology and Internal Medicine at Saint Louis University School of Medicine (United States) under the mentorship of Prof. Ratna B. Ray and Prof. Ranjit Ray, respectively. He returned to Japan and became an Associate Professor in the Department of Gastroenterology and Nephrology at Chiba University, Graduate School of Medicine in 2008. In his current roles as Associate Professor and Clinical Professor in the Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine at Itabashi-ku, Tokyo, Japan, he performs clinical and basic research on hepatic and pancreatic diseases. (L-Editor: Filipodia)

**AIMS AND SCOPE**

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

**INDEXING/ABSTRACTING**

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for WJG as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Yu-Jie Ma; Production Department Director: Xiang Li; Editorial Office Director: Ze-Mao Gong.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski, Subrata Ghosh

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

August 21, 2020

**COPYRIGHT**

© 2020 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Risk of malignancy in Caroli disease and syndrome: A systematic review

René Fahrner, Sandra GC Dennler, Daniel Inderbitzin

**ORCID number:** René Fahrner 0000-0002-7129-5905; Sandra GC Dennler 0000-0002-8020-0349; Daniel Inderbitzin 0000-0002-6098-9338.

**Author contributions:** Fahrner R was involved in the conceptualization, data curation, investigation, project administration, writing-original draft; Dennler SGC was involved in the conceptualization, data curation, investigation, writing review and editing; Inderbitzin D was involved in the conceptualization, data curation, investigation, writing review and editing. All authors have read and approve the final manuscript.

**Conflict-of-interest statement:**

There are no conflicts of interest.

**PRISMA 2009 Checklist statement:**

The authors have read the PRISMA 2009 checklist, and the manuscript was prepared and revised accordingly.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,

**René Fahrner, Daniel Inderbitzin**, Department of Surgery, Bürgerspital Solothurn, Solothurn 4500, Switzerland

**Sandra GC Dennler**, Department of Surgery, University Hospital Dresden, Dresden 01307, Germany

**Corresponding author:** René Fahrner, MD, Surgeon, Department of Surgery, Bürgerspital Solothurn, Schöngrünstrasse 42, Solothurn 4500, Switzerland. [rene.fahrner@spital.so.ch](mailto:rene.fahrner@spital.so.ch)

### Abstract

#### BACKGROUND

Congenital intrahepatic bile duct dilatation without fibrosis is called Caroli disease (CD), and is called Caroli syndrome (CS) when it has fibrotic and cirrhotic liver morphology. The development of intrahepatic carcinoma is described in both conditions, but the reported incidence varies extensively. Potential risk factors for the malignant transformation were not described. Furthermore, conservative or surgical treatment is performed depending on the extent of cystic malformation, hepatic dysfunction and structural hepatic changes, but little is known about which treatment should be offered to patients with CD or CS and cancer.

#### AIM

To further investigate the malignant transformation in these conditions.

#### METHODS

A systematic review of the current literature until January 2019 was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A search using Medline (PubMed) was performed using a combination of Medical Subject Headings terms "caroli disease", "caroli syndrome", "tumor", "malignant", and "cholangiocarcinoma". Only human studies published in English were used for this systematic review. The following parameters were extracted from each article: year of publication, type of study, number of patients, incidence of malignant tumor, duration of symptoms, age, sex, diagnostics, identification of tumor, surgical therapy, survival and tumor recurrence.

#### RESULTS

Twelve retrospective studies reporting the courses of 561 patients (53% females) were included in this systematic review. With a mean age of 41.6 years old (range

and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Received:** January 20, 2020

**Peer-review started:** January 20, 2020

**First decision:** February 27, 2020

**Revised:** May 15, 2020

**Accepted:** August 1, 2020

**Article in press:** August 1, 2020

**Published online:** August 21, 2020

**P-Reviewer:** Bugaj AM

**S-Editor:** Zhang H

**L-Editor:** A

**P-Editor:** Ma YJ



23 to 56 years old), patients were younger than other populations undergoing liver surgery. Depending on the size of the study population the incidence of cholangiocarcinoma varied from 2.7% to 37.5% with an overall incidence of 6.6%. There were only few detailed reports about preoperative diagnostic work-up, but a multimodal work-up including ultrasound of the liver, computed tomography, magnetic resonance imaging and endoscopic retrograde cholangiopancreatography was used in most studies. Disease duration was variable with up to several years. Most patients had episodes of cholangitis, sepsis, fever or abdominal pain. Tumor detection was an incidental finding of the surgical specimen in most cases because it is currently often impossible to detect tumor manifestation during preoperative diagnostics. Liver resection or liver transplantation was performed depending on the extent of the biliary pathology and additional alterations of the liver structure or function. No postoperative adjuvant chemotherapy was reported, but chemotherapy was administered in selected cases of tumor recurrence. Overall survival rates after one year were low at 36% and a high recurrence rate of up to 75% during the observation period.

## CONCLUSION

Only few retrospective studies reported a low tumor incidence. Despite the high rate of mortality and tumor recurrence, definite surgical treatment should be offered as soon as possible.

**Key words:** Malignancy; Caroli disease; Caroli syndrome; Tumor; Cholangiocarcinoma; Review

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Congenital intrahepatic bile duct dilatation with or without fibrosis is called Caroli syndrome or Caroli disease, respectively. We performed a systematic review of the current literature to investigate the incidence of malignant transformation, risk factors, and surgical treatment options. There were only 12 retrospective cohort studies reporting 561 patients, including 37 patients with malignancy, so an exact preoperative diagnostic work-up, risk factors and preferred surgical treatment were impossible to conclude due to lack of data. Overall survival rates after one year were low (36%), and recurrence rate was high (75%) during the observation period.

**Citation:** Fahrner R, Dennler SG, Inderbitzin D. Risk of malignancy in Caroli disease and syndrome: A systematic review. *World J Gastroenterol* 2020; 26(31): 4718-4728

**URL:** <https://www.wjgnet.com/1007-9327/full/v26/i31/4718.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v26.i31.4718>

## INTRODUCTION

Vachell first described Caroli disease (CD) in 1906<sup>[1]</sup>. The segmental dilatation of the intrahepatic biliary ducts in combination with renal cystic disease and liver fibrosis is named Caroli syndrome (CS)<sup>[2,3]</sup>. Due to focal inflammation, likely initiated by an intrauterine malformation of the bile ductal plate, the biliary tract is continuously destroyed over decades<sup>[4,5]</sup>. Consequently, the further progression of this destructive inflammatory state leads to recurrent episodes of cholangitis, the development of biliary stones and malignant transformation in some cases, and cholangiocarcinoma is described, but is rare overall with reports up to 14%<sup>[5-7]</sup>. However, the risk of developing intrahepatic cholangiocellular carcinoma in CD or CS is increased 100-fold compared to healthy individuals<sup>[8]</sup>. The association between intrahepatic cystic lesions in CS or CD and cholangiocarcinoma was first published in 1968<sup>[9]</sup>. The distinct etiology of this association and malformation is not clear<sup>[8]</sup>, but several theories are postulated: Carcinogenic component of the bile with prolonged effect during biliary stasis<sup>[8]</sup>; permanent stone irritation and formation of carcinogens<sup>[10]</sup>; and cellular predisposition for neoplastic change of the congenital cystic malformation of the biliary tract<sup>[8]</sup>. Unfortunately, the preoperative diagnosis of malignant transformation is difficult, and final diagnosis of the cholangiocarcinoma is typically made during

pathological examination of the surgical specimen and less common in preoperative liver biopsies<sup>[6,11,12]</sup>. Furthermore, malignancy in CS or CD is suggested to be more likely in older patients<sup>[11]</sup>, insufficient bile drainage<sup>[8]</sup> and long disease duration<sup>[8,10,12]</sup>. Therefore, the time span between the onset of first symptoms and definitive treatment is up to 60 mo in many cases<sup>[13,14]</sup>. The complaint symptoms may be unspecific and vary from pain, pruritus, fever, sepsis, recurrent cholangitis, abscesses, pancreatitis, weight loss, and adynamia<sup>[3,5,15-22]</sup>. Besides biliary drainage operations or interventions<sup>[7,22-24]</sup>, liver resection<sup>[7,12,25]</sup> or orthotopic liver transplantation (OLT)<sup>[7]</sup> are performed. The decision to perform a specific intervention depends on the extent of biliary pathology and hepatic fibrosis and portal hypertension consecutively.

The present systematic review (1) analyzed the existing literature on the current incidence of malignancy in CS or CD; (2) the potential risk factors for the development of malignancy in patients with CS or CD; (3) the postoperative outcome of CS or CD after liver resection or OLT; and (4) the best treatment options for patients with CS or CD and suspected malignancy.

## MATERIALS AND METHODS

A systematic review of the literature until January 2019 was performed according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement<sup>[26]</sup> to identify studies reporting the incidence of tumors in patients with CS and CD underwent resection or liver transplantation. Therefore, a literature search was performed using Medline (PubMed) from January 1993 to January 2019. During screening process, non-English articles were excluded. Reports with less than five patients and review articles were excluded. The search was performed using a combination of Medical Subject Headings terms “caroli disease”, “caroli syndrome”, “tumor”, “malignant”, and “cholangiocarcinoma”. Only human studies were used for this systematic review. The titles and abstracts of the articles were screened first for scientific relevance of this review. The full article was reviewed for potential eligibility and reported incidence of malignancy in the next step. The flow-chart show the process of identification, screening and final inclusion of articles in [Figure 1](#).

The following parameters were extracted from each article: Year of publication, type of study, number of patients with CD or CS, incidence of malignant tumor, duration of symptoms (months), age in years, sex (females *vs* males), used diagnostics (ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous cholangiography), identification of tumor (preoperative biopsy or incidental finding), surgical therapy (liver resection, OLT), survival and tumor recurrence.

## RESULTS

### Included studies

Twelve manuscripts were included in this systematic review ([Table 1](#)). All studies were of a retrospective nature. Most studies were single-center studies ( $n = 8$ ), and four studies included data of an official registry ( $n = 2$ ) or multicenter ( $n = 2$ ) analysis. The study populations of each study were small, with only three studies including more than 100 patients and 75% of the studies included less than 45 patients, with a total of 561 patients. The reported incidence of cholangiocarcinoma in patients treated for CS or CD varied from 2.7% to 37.5%, depending on the size of the study population. The overall incidence of cholangiocarcinoma in all included patients was 6.6% ( $n = 37$ ).

### Diagnostic preoperative work-up

Only few studies reported a detailed preoperative diagnostic work-up for patients with CS and CD in general, and no study presented a work-up to identify cholangiocarcinoma within CS and CD ([Table 2](#)). Ultrasound of the liver, CT, MRI, and ERCP revealed the standard of preoperative diagnostics in most of the studies. Three studies reported percutaneous cholangiography to estimate the extent of biliary pathology.

### Patient demographics

There was a slight predominance of female sex in all patients (53% females, [Table 3](#)).

**Table 1 Literature search results and analyzed manuscripts**

| Ref.                                      | Country        | Year of publication | Type of study                | n of reported patients | n of cancer (%) |
|-------------------------------------------|----------------|---------------------|------------------------------|------------------------|-----------------|
| Ammori <i>et al</i> <sup>[27]</sup>       | United Kingdom | 2002                | Single-center, retrospective | 8                      | 3 (37.5)        |
| De Kerckhove <i>et al</i> <sup>[19]</sup> | Belgium        | 2005                | ELTR registry, retrospective | 113                    | 3 (2.7)         |
| Kassahun <i>et al</i> <sup>[21]</sup>     | Germany        | 2005                | Single-center, retrospective | 33                     | 3 (9)           |
| Habib <i>et al</i> <sup>[17]</sup>        | United States  | 2006                | Single-center, retrospective | 33                     | 1 (3)           |
| Bockhorn <i>et al</i> <sup>[30]</sup>     | Germany        | 2006                | Single-center, retrospective | 12                     | 3 (25)          |
| Millwala <i>et al</i> <sup>[5]</sup>      | United States  | 2008                | UNOS registry, retrospective | 104                    | 3 (2.9)         |
| Ulrich <i>et al</i> <sup>[3]</sup>        | Germany        | 2008                | Single-center, retrospective | 44                     | 4 (9)           |
| Hori <i>et al</i> <sup>[24]</sup>         | Japan          | 2010                | Single-center, retrospective | 5                      | 1 (20)          |
| Lendoire <i>et al</i> <sup>[13]</sup>     | Argentina      | 2011                | Multicenter, retrospective   | 24                     | 1 (4.2)         |
| Mabrut <i>et al</i> <sup>[20]</sup>       | France         | 2013                | Multicenter, retrospective   | 155                    | 8 (5)           |
| Moslim <i>et al</i> <sup>[12]</sup>       | United States  | 2015                | Single-center, retrospective | 9                      | 3 (33.3)        |
| Fahrner <i>et al</i> <sup>[25]</sup>      | Germany        | 2018                | Single-center, retrospective | 21                     | 4 (19)          |

ELTR: European Liver Transplant Registry; UNOS: United Network of Organ Sharing.

**Table 2 Diagnostic work flow prior to surgery**

| Ref.                                      | CT      | MRI     | ERCP    | Ultrasound | Others                       |
|-------------------------------------------|---------|---------|---------|------------|------------------------------|
| Ammori <i>et al</i> <sup>[27]</sup>       | Yes     | Yes     | 100%    | Yes        | No data                      |
| De Kerckhove <i>et al</i> <sup>[19]</sup> | Yes     | Yes     | Yes     | Yes        | Percutaneous cholangiography |
| Kassahun <i>et al</i> <sup>[21]</sup>     | 100%    | 16.2%   | 83.9%   | 100%       | No data                      |
| Habib <i>et al</i> <sup>[17]</sup>        | No data | No data | No data | No data    | No data                      |
| Bockhorn <i>et al</i> <sup>[30]</sup>     | 100%    | No data | 92%     | 100%       | No data                      |
| Millwala <i>et al</i> <sup>[5]</sup>      | No data | No data | No data | No data    | No data                      |
| Ulrich <i>et al</i> <sup>[3]</sup>        | Yes     | Yes     | Yes     | Yes        | Percutaneous cholangiography |
| Hori <i>et al</i> <sup>[24]</sup>         | No data | No data | No data | No data    | No data                      |
| Lendoire <i>et al</i> <sup>[13]</sup>     | Yes     | Yes     | Yes     | Yes        | Percutaneous cholangiography |
| Mabrut <i>et al</i> <sup>[20]</sup>       | No data | 74.7%   | 27.7%   | No data    | No data                      |
| Moslim <i>et al</i> <sup>[12]</sup>       | No data | No data | No data | No data    | No data                      |
| Fahrner <i>et al</i> <sup>[25]</sup>      | No data | No data | No data | No data    | No data                      |

Percentages given indicate frequency of diagnostic tool within the study. CT: Computed tomography; MRI: Magnetic resonance imaging; ERCP: Endoscopic retrograde cholangiopancreatography.

Patients suffering from CS or CD are younger than other populations undergoing liver resection, for *e.g.*, liver cancer, the mean patient age ranged from 23 to 56 years old, with a total mean of 41.6 years old at the time point of surgery. Only five studies reported data on the duration of disease or symptoms. Patients reported at least 7 mo of mean duration of symptoms, but the most patients suffered from cholangitis, fever or abdominal pain for several years (Table 3). In most cases (89%), tumor identification was finally made in definitive histological assessment as an incidental finding. The diagnosis was suspected prior surgery or proven by preoperative biopsy only in less than five patients (14%).

### **Tumor treatment and survival**

Patients with CS or CD were treated via liver resection or OLT (Table 4). The indication for the onco-surgical treatment (liver resection or OLT) was primarily based

**Table 3 Patient demographics, duration of disease and tumor identification**

| Ref.                                      | Age (yr) | Female sex (%) | Duration of disease                | Tumor identification                                         |
|-------------------------------------------|----------|----------------|------------------------------------|--------------------------------------------------------------|
| Ammori <i>et al</i> <sup>[27]</sup>       | 35       | 75             | No data                            | No data                                                      |
| De Kerckhove <i>et al</i> <sup>[19]</sup> | 39.7     | 52             | No data                            | No data                                                      |
| Kassahun <i>et al</i> <sup>[21]</sup>     | 51.5     | 55             | < 1 yr 51%, 1-5 yr 13%, > 5 yr 35% | No data                                                      |
| Habib <i>et al</i> <sup>[17]</sup>        | 26       | 50             | No data                            | No data                                                      |
| Bockhorn <i>et al</i> <sup>[30]</sup>     | 39       | 42             | No data                            | 67% incidental finding                                       |
| Millwala <i>et al</i> <sup>[5]</sup>      | 35       | 55             | No data                            | No data                                                      |
| Ulrich <i>et al</i> <sup>[3]</sup>        | 49       | 55             | < 1 yr 55%, > 5 yr 2.5%            | 100% incidental finding                                      |
| Hori <i>et al</i> <sup>[24]</sup>         | 23.74    | No data        | 6.4 yr                             | 100% puncture of nodule prior surgery                        |
| Lendoire <i>et al</i> <sup>[13]</sup>     | 48.7     | 70             | 2.6 yr                             | 100% incidental finding                                      |
| Mabrut <i>et al</i> <sup>[20]</sup>       | 55.7     | 43             | 7 mo                               | No data                                                      |
| Moslim <i>et al</i> <sup>[12]</sup>       | 40       | 22             | No data                            | 100% incidental finding                                      |
| Fahrner <i>et al</i> <sup>[25]</sup>      | 56       | 74             | No data                            | 75% incidental finding 25% suspicious nodules in diagnostics |

**Table 4 Surgical treatment, tumor characteristics and survival**

| Ref.                                      | Surgery for all patients (LR vs OLT) <sup>1</sup> | TNM                                                    | 1-yr survival cancer patients | Recurrence                 |
|-------------------------------------------|---------------------------------------------------|--------------------------------------------------------|-------------------------------|----------------------------|
| Ammori <i>et al</i> <sup>[27]</sup>       | 50% vs 50%                                        | No data                                                | 33%                           | 0%                         |
| De Kerckhove <i>et al</i> <sup>[19]</sup> | 0% vs 100%                                        | No data                                                | 66%                           | 33%                        |
| Kassahun <i>et al</i> <sup>[21]</sup>     | 87% vs 0%                                         | No data                                                | 0%                            | 33%                        |
| Habib <i>et al</i> <sup>[17]</sup>        | 0% vs 100%                                        | No data                                                | 0%                            | No data                    |
| Bockhorn <i>et al</i> <sup>[30]</sup>     | 83% vs 17%                                        | <i>n</i> = 1 pT1, <i>n</i> = 1 pT2                     | 66%                           | 0%                         |
| Millwala <i>et al</i> <sup>[5]</sup>      | 0% vs 100%                                        | No data                                                | 0%                            | No data                    |
| Ulrich <i>et al</i> <sup>[3]</sup>        | 90% vs 10%                                        | No data                                                | 0%                            | No data                    |
| Hori <i>et al</i> <sup>[24]</sup>         | 0% vs 100%                                        | No data                                                | No data                       | No data                    |
| Lendoire <i>et al</i> <sup>[13]</sup>     | 91.6% vs 0%                                       | No data                                                | 100%                          | No data                    |
| Mabrut <i>et al</i> <sup>[20]</sup>       | 75% vs 18.9%                                      | <i>n</i> = 6 R0, <i>n</i> = 1 peritoneal seeding       | 33%                           | 50%                        |
| Moslim <i>et al</i> <sup>[12]</sup>       | 22% vs 78%                                        | No data                                                | 0%                            | 33%, 66% tumor progression |
| Fahrner <i>et al</i> <sup>[25]</sup>      | 90% vs 10%                                        | <i>n</i> = 1 pT1N1, <i>n</i> = 2 pT2, <i>n</i> = 1 pT3 | 100%                          | 75%                        |

<sup>1</sup>Besides liver resection and orthotopic liver transplantation, other surgical interventions performed, so that the sum of the percentages does not equal 100%. LR: Liver resection; OLT: Orthotopic liver transplantation; TNM: Tumor-nodes-metastases.

on the extent of the biliary pathology and an additional alteration of the liver structure or function. Most of the tumors were incidental findings, and no exact proposal of liver resection or liver transplantation was possible on the basis of the data, but the proposed treatment of cholangiocarcinomas without CS or CD is likely applicable in these patients. In cases of tumor identification in histological assessment of the surgical specimen, no postoperative adjuvant chemotherapy was reported. Chemotherapy was administered in selected cases of tumor recurrence. Unfortunately, few data were available on the tumor-node-metastasis (TNM) classification or grading of the tumors. Most tumors were localized within in the liver (pT1 or pT2), but local lymph node involvement or peritoneal seeding was described (Table 4). However, overall survival rates after one year were low at 36% in total. It was impossible to distinguish the effect of liver resection or liver transplantation due to the retrospective reports of both different surgical treatments. The reported recurrence rate during the observation

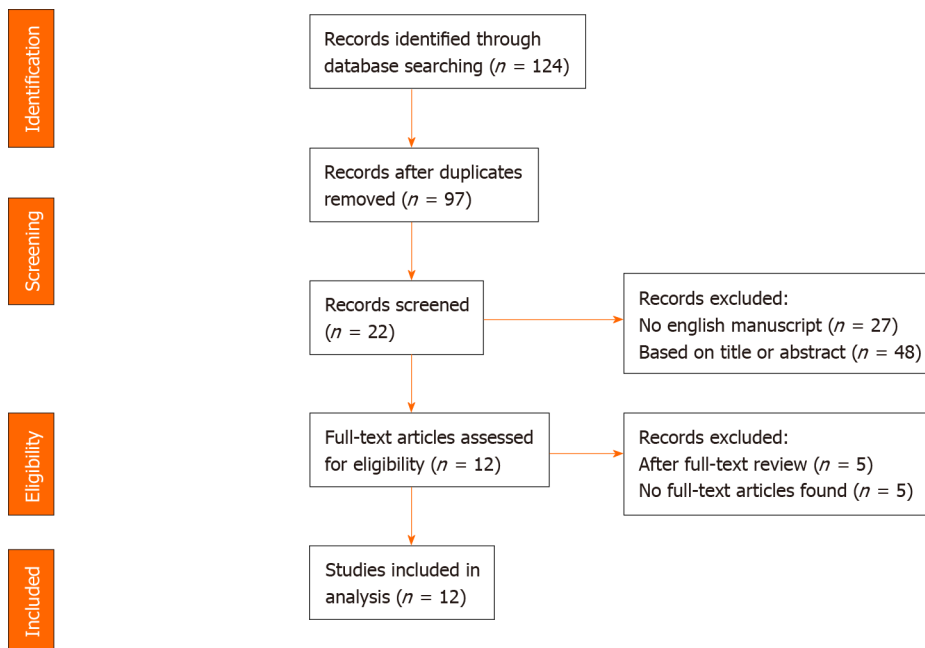


Figure 1 Flow-chart of the identification, screening and final inclusion of articles.

period in 7 studies was high, at up to 75%.

## DISCUSSION

Only a few reports investigated CS and CD and the development of cancer, and there was no suitable explanation for this fact in most of the publications. The present review analyzed the data of 561 patients included in 12 studies who were treated either with liver resection or OLT. Unfortunately, most of the studies were reports of less than 45 patients, and retrospective single or multicenter experiences were reported over several years in all cases. In addition, various case reports were not included in this systematic review.

The total incidence of cancerous transformation or simultaneous cancer in CS and CD is approximately 7%, but it ranged from approximately 3% to almost 40% in the beginning of the 2000s depending on the cohort<sup>[19,27]</sup>. Over time this incidence did not change, and the latest publications during the last six years reported incidences between 5% to 33%<sup>[12,20,25]</sup>. There were no new aspects reported on the development of cancerous transformation, and biliary stasis<sup>[8]</sup>, stone irritation<sup>[10]</sup>, a cellular predisposition of the cystic congenital malformation<sup>[8]</sup> and a combination of these factors are possible pathways<sup>[28]</sup>. Most cases of cancer are cholangiocarcinoma or adenocarcinoma, and the biliary epithelium is propagated as the origin of the cancerous transformation<sup>[6]</sup>. As one trigger for the malignant transformation, chronic inflammation of the biliary epithelium during cholangitis with consecutive dysplasia and carcinogenesis is postulated<sup>[29]</sup>. Unfortunately, due to little data, the hypothesis of an increased incidence for malignant transformation in large bile ducts rather than in small peripheral ducts could not be proven in this review<sup>[14]</sup>.

There are only few data on the structured preoperative work-up of patients with CS and CD regarding the used method. Ultrasound was used in most studies to identify cystic lesions within the liver and potential altered liver structure, such as liver cirrhosis<sup>[21,30]</sup>. To further evaluate the biliary tract, ERCP or percutaneous cholangiography was used in selected cases in some of the studies<sup>[3,13,19,27]</sup>. However, the use of invasive biliary diagnostics should be avoided and performed only in selected patients because they are often associated with an increased risk for infections<sup>[19]</sup>. If reported, CT or MRI scans were used to investigate the nature of the cysts, identify possible malignant transformation, and plan and assess the surgical resectability<sup>[20,21,27]</sup>. The tumor markers Ca-19-9 is often elevated in cases of benign biliary obstruction or cholangitis, and higher levels may mislead the correct diagnosis<sup>[7]</sup>. Overall, the diagnosis of malignancy in CS and CD is difficult, and the tumor identification was an incidental finding in most of the reports in this review, which was made during the

final histological assessment of the surgical specimen, because the preoperative identification of a tumor within a dilated cystic bile tract is almost impossible<sup>[3,8,11,13,25]</sup>. Therefore, the value of screening patients with CS and CD for malignancy is quite inaccurate, and definite treatment should be sought, because delayed diagnosis and widespread tumor are associated with a poor prognosis<sup>[18]</sup>. In the future, a more aggressive diagnostic work-up including endoscopic ultrasound, puncture of suspected segments within the biliary tract, cholangioscopy (percutaneously) should be used, with the goal to detect more frequently patients with malignant transformation and therefore avoiding delay of definite surgical treatment.

The initial treatment of CS and CD is often nonsurgical and supportive therapy using analgesia, antibiotics in case of biliary infections and ursodeoxycholic acid<sup>[31,32]</sup>. Surgical or interventional drainage procedures may be performed to remove biliary tract obstructions and improve biliary passage to decrease the risk and burden of cholangitis<sup>[33,34]</sup>. Beside this conservative treatment, the final diagnosis of CS or CD often takes months or years until the patient is referred for definite surgical treatment. During that time, patients suffer recurrent infections, sepsis, hepatic abscesses, portal hypertension, and the risk of malignant transformation without solving the problem of the dilated and cystic biliary tract<sup>[30,35-38]</sup>. There are reports that malignant transformation does not depend on the disease duration, because cancer occurred in patients with symptomatic CS or CD of two months to two decades. Therefore, it has been postulated that there are likely more aggressive subgroups in CS or CD with increased potential for malignancy<sup>[30]</sup>. Due to a lack of data, there is no explanation or postulated pathway for this fact.

As a conclusion for this observation, surgical treatment with liver resection or OLT should be offered to patients with CS or CD as soon as possible to avoid recurrent sepsis and primarily malignant transformation<sup>[3,25,30]</sup>. In cases of conservative treatment, even asymptomatic patients should be regularly screened clinically and radiologically for malignancy<sup>[30]</sup>. To obtain the best treatment and surveillance, an interdisciplinary management team, including surgeons, gastroenterologists, hepatologists, radiologists, pediatrician and specialists in infectious diseases, is needed. Therefore, these patients are often treated in transplant centers. Overall, a high suspicion for potential malignant transformation is needed, and early treatment should be intended.

After one year, the survival rate of all tumor patients was 35%, which is low and much lower than in hepatocellular carcinoma patients<sup>[39-41]</sup> or selected surgical treated cholangiocarcinoma patients<sup>[42-45]</sup>. At least 32% had tumor recurrence during the observation period, but five studies did not report any data about recurrence. Therefore, the incidence may be even higher, and some patients likely died before the detection of any tumor recurrence probably due to the high mortality rate. In some studies, a high morbidity and in-house mortality was reported after OLT due to infectious complications and therapy-resistant sepsis<sup>[17,21]</sup>. The general treatment suggestion is to perform liver resection in defined and localized cystic degeneration and evaluate OLT in diffuse cystic affection with structural hepatic changes<sup>[3,25,27,30]</sup>.

On the basis of the data, no adjuvant chemotherapy was administered in cases of cholangiocarcinoma or adenocarcinoma. There were only a few reports of chemotherapy in cases of recurrence when surgery was no longer an option. This result is comparable to patients with cholangiocarcinoma without CS or CD, where chemotherapy is used only in nonresectable and extended tumors or recurrence<sup>[46]</sup>.

The studies were not comparable. For example, TNM staging was available only in a few studies. The extent of cystic degeneration and underlying structural liver changes greatly influences the choice of treatment as mentioned previously. In cases of cancer in CS patients treated with OLT, the long-term survival rate was 0%<sup>[17,27]</sup>, and recurrence rates were high, which are comparable to studies of OLT and cholangiocarcinoma without CS or CD<sup>[47]</sup>. Patients with localized and small cholangiocarcinoma likely benefit from OLT, although little current data exist<sup>[7]</sup>.

The following limitations of this systematic review must be addressed. Overall, there were predominantly small, retrospective cohort studies with nonhomogeneous patient collectives treated with liver resection or OLT. Therefore, it was not possible to identify specific risk factors indicating the risk for malignant transformation in CS or CD, because these two entities were not reported separately. Another aspect was that most of the tumors were incidental findings, so a specific work-up algorithm is likely not possible to define. Further prospective and multicenter studies or databases with the specific goal to identify risk factors for malignant transformation are needed.

In conclusion, there were only few retrospective studies of patients treated with surgery in cases of CS and CD. Therefore, it was not possible to identify valuable risk factors for the malignant transformation in these patients. On the other hand, the previously postulated factors for the development of malignancy could neither be

proven nor rebutted. Overall, the incidence of simultaneous malignancy in CS or CD is low, but high tumor rates to almost 40% were reported depending on the investigated cohort. Because a high proportion of malignant tumors were incidental findings, the definite surgical treatment should be offered as soon as possible to avoid septic complications and the development of carcinoma. Surgical treatment should include liver resection in localized affection (primarily CD) and OLT in diffuse affection and structural liver changes, such as liver fibrosis (CS). In proven malignant transformation, small tumors may be treated with OLT successfully, but extensive tumors are mostly associated with an inferior outcome, *e.g.*, due to tumor recurrence. Overall, the postoperative results are associated with a high rate of mortality and tumor recurrence. Therefore, patient selection and the timing of surgery are of high importance. On the basis of the current literature, there are no optimal screening methods described to identify patients with malignant transformation early and safely. Therefore, a high suspicion of malignancy is needed to find the exact time point for surgery and avoid delay in definite surgical treatment. Finally, new screening tools are needed to increase the rate of tumor identification during long-term surveillance of patients with CS or CD.

## ARTICLE HIGHLIGHTS

### Research background

Congenital intrahepatic bile duct dilatation without fibrosis is called Caroli disease (CD), and is called Caroli syndrome (CS) when it has fibrotic and cirrhotic liver morphology. The development of intrahepatic carcinoma is described in both conditions, but the reported incidence varies extensively. Furthermore, there are no valid guidelines how to treat and diagnose malignant transformation in these patients.

### Research motivation

So far no valid potential risk factors for the malignant transformation were described. Furthermore, conservative or surgical treatment is performed depending on the extent of cystic malformation, hepatic dysfunction and structural hepatic changes, but little is known about which treatment should be offered to patients with CD or CS and especially cancer.

### Research objectives

We performed a systematic review of the current literature to investigate specific conditions for malignant transformation in patients with CD and CS and to identify potential risk factors and recommendations regarding diagnosis and surgical treatment.

### Research methods

A systematic review of the current literature until January 2019 was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. During screening process, non-English articles and reports with less than five patients were excluded. The search was performed using a combination of Medical Subject Headings terms “caroli disease”, “caroli syndrome”, “tumor”, “malignant”, and “cholangiocarcinoma”. Only human studies were used for this systematic review.

### Research results

Twelve retrospective studies reporting the courses of 561 patients (53% females) were included in this systematic review. The patients' mean age was 41.6 years old (range 23 to 56 years old), therefore patients were younger than other populations undergoing liver surgery. The incidence of cholangiocarcinoma varied from 2.7% to 37.5% with an overall incidence of 6.6%. There were only few detailed reports about preoperative diagnostic work-up. Disease duration was variable with up to several years. In most cases tumor detection was an incidental finding of the surgical specimen as tumor detection in preoperative diagnostics was often impossible. Surgical treatment depended on the extent of the biliary pathology and additional alterations of the liver structure or function. No adjuvant chemotherapy was reported. Overall survival rates after one year were low at 36% and a high recurrence rate of up to 75% during the observation period was seen.

## Research conclusions

Only few retrospective studies are available and reported a low tumor incidence. On the basis of these studies distinct suggestions regarding diagnosis and treatment are impossible to define. Despite the high rate of mortality and tumor recurrence, definite surgical treatment should be offered as soon as possible.

## Research perspectives

Further prospective multicenter investigations regarding patient surveillance, diagnostic tools, time point of surgery and risk factors of malignant transformation are needed.

## REFERENCES

- 1 Vachell HR, Stevens WM. CASE OF INTRAHEPATIC CALCULI. *Br Med J* 1906; **1**: 434-436 [PMID: 20762542 DOI: 10.1136/bmj.1.2356.434]
- 2 Caroli J, Soupault R, Kossakowski J, Plocker L, Paradowska. [Congenital polycystic dilation of the intrahepatic bile ducts; attempt at classification]. *Sem Hop* 1958; **34**: 488-95/SP [PMID: 13543375]
- 3 Ulrich F, Pratschke J, Pascher A, Neumann UP, Lopez-Hänninen E, Jonas S, Neuhaus P. Long-term outcome of liver resection and transplantation for Caroli disease and syndrome. *Ann Surg* 2008; **247**: 357-364 [PMID: 18216545 DOI: 10.1097/SLA.0b013e31815cca88]
- 4 Desmet VJ. Congenital diseases of intrahepatic bile ducts: variations on the theme "ductal plate malformation". *Hepatology* 1992; **16**: 1069-1083 [PMID: 1398487 DOI: 10.1002/hep.1840160434]
- 5 Millwala F, Segev DL, Thuluvath PJ. Caroli's disease and outcomes after liver transplantation. *Liver Transpl* 2008; **14**: 11-17 [PMID: 18161799 DOI: 10.1002/lt.21366]
- 6 Balsells J, Margarit C, Murio E, Lazaro JL, Charco R, Vidal MT, Bonnin J. Adenocarcinoma in Caroli's disease treated by liver transplantation. *HPB Surg* 1993; **7**: 81-6; discussion 86-7 [PMID: 8260439 DOI: 10.1155/1993/61048]
- 7 Lai Q, Lerut J. Proposal for an algorithm for liver transplantation in Caroli's disease and syndrome: putting an uncommon effort into a common task. *Clin Transplant* 2016; **30**: 3-9 [PMID: 26385435 DOI: 10.1111/ctr.12640]
- 8 Dayton MT, Longmire WP Jr, Tompkins RK. Caroli's Disease: a premalignant condition? *Am J Surg* 1983; **145**: 41-48 [PMID: 6295196 DOI: 10.1016/0002-9610(83)90164-2]
- 9 Schiewe R, Baudisch E, Ehrhardt G. [Congenital intrahepatic bile duct cysts with calcinosis and malignant degenerations]. *Bruns Beitr Klin Chir (1971)* 1968; **216**: 264-271 [PMID: 4302452]
- 10 Flanigan DP. Biliary carcinoma associated with biliary cysts. *Cancer* 1977; **40**: 880-883 [PMID: 890668 DOI: 10.1002/1097-0142(197708)40:2<880::AID-CNCR2820400242>3.0.CO;2-X]
- 11 Vlachogiannakos J, Potamianos S, Triantos C, Makri I, Imvrios G, Patsiaoura K, Avgerinos A. Monolobar Caroli's disease complicated by cholangiocarcinoma in a 70-year-old man, previously asymptomatic. *Gastrointest Endosc* 2004; **60**: 297-300 [PMID: 15278068 DOI: 10.1016/s0016-5107(04)01572-x]
- 12 Moslim MA, Gunasekaran G, Vogt D, Cruise M, Morris-Stiff G. Surgical Management of Caroli's Disease: Single Center Experience and Review of the Literature. *J Gastrointest Surg* 2015; **19**: 2019-2027 [PMID: 26302876 DOI: 10.1007/s11605-015-2918-9]
- 13 Lendoire JC, Raffin G, Grondona J, Bracco R, Russi R, Ardiles V, Gondolesi G, Defelitto J, de Santibañes E, Imventarza O. Caroli's disease: report of surgical options and long-term outcome of patients treated in Argentina. Multicenter study. *J Gastrointest Surg* 2011; **15**: 1814-1819 [PMID: 21796462 DOI: 10.1007/s11605-011-1620-9]
- 14 Mabrut JY, Partensky C, Jaeck D, Oussoultzoglou E, Baulieux J, Boillot O, Lerut J, de Ville de Goyet J, Hubert C, Otte JB, Audet M, Ducerf C, Gigot JF. Congenital intrahepatic bile duct dilatation is a potentially curable disease: long-term results of a multi-institutional study. *Ann Surg* 2007; **246**: 236-245 [PMID: 17667502 DOI: 10.1097/SLA.0b013e3180f61abf]
- 15 Clemente G, Giuliani F, De Rose AM, Ardito F, Giovannini I, Nuzzo G. Liver resection for intrahepatic stones in congenital bile duct dilatation. *J Visc Surg* 2010; **147**: e175-e180 [PMID: 20709617 DOI: 10.1016/j.jvisc.2010.06.005]
- 16 Taylor AC, Palmer KR. Caroli's disease. *Eur J Gastroenterol Hepatol* 1998; **10**: 105-108 [PMID: 9581983 DOI: 10.1097/00042737-199802000-00001]
- 17 Habib S, Shakil O, Couto OF, Demetris AJ, Fung JJ, Marcos A, Chopra K. Caroli's disease and orthotopic liver transplantation. *Liver Transpl* 2006; **12**: 416-421 [PMID: 16498655 DOI: 10.1002/lt.20719]
- 18 Abdalla EK, Forsmark CE, Lauwers GY, Vauthey JN. Monolobar Caroli's Disease and cholangiocarcinoma. *HPB Surg* 1999; **11**: 271-6; discussion 276-7 [PMID: 10468120 DOI: 10.1155/1999/70985]
- 19 De Kerckhove L, De Meyer M, Verbaandert C, Mourad M, Sokal E, Goffette P, Geubel A, Karam V, Adam R, Lerut J. The place of liver transplantation in Caroli's disease and syndrome. *Transpl Int* 2006; **19**: 381-388 [PMID: 16623873 DOI: 10.1111/j.1432-2277.2006.00292.x]
- 20 Mabrut JY, Kianmanesh R, Nuzzo G, Castaing D, Boudjema K, Létoublon C, Adham M, Ducerf C, Pruvot FR, Meurisse N, Cherqui D, Azoulay D, Capussotti L, Lerut J, Reding R, Mentha G, Roux A, Gigot JF. Surgical management of congenital intrahepatic bile duct dilatation, Caroli's disease and syndrome: long-term results of the French Association of Surgery Multicenter Study. *Ann Surg* 2013; **258**: 713-21; discussion 721 [PMID: 24121258 DOI: 10.1097/SLA.0000000000000269]
- 21 Kassahun WT, Kahn T, Wittekind C, Mössner J, Caca K, Hauss J, Lamesch P. Caroli's disease: liver resection and liver transplantation. Experience in 33 patients. *Surgery* 2005; **138**: 888-898 [PMID: 16291390 DOI: 10.1016/j.surg.2005.05.002]
- 22 Jarufe N, Figueroa E, Muñoz C, Moisan F, Varas J, Valbuena JR, Bambs C, Martínez J, Pimentel F.

- Anatomic hepatectomy as a definitive treatment for hepatolithiasis: a cohort study. *HPB (Oxford)* 2012; **14**: 604-610 [PMID: 22882197 DOI: 10.1111/j.1477-2574.2012.00488.x]
- 23 **Otani K**, Shimizu S, Chijiwa K, Ogawa T, Morisaki T, Sugitani A, Yamaguchi K, Tanaka M. Comparison of treatments for hepatolithiasis: hepatic resection versus cholangioscopic lithotomy. *J Am Coll Surg* 1999; **189**: 177-182 [PMID: 10437840 DOI: 10.1016/s1072-7515(99)00109-x]
  - 24 **Hori T**, Oike F, Ogura Y, Ogawa K, Hata K, Yonekawa Y, Ueda M, Sakamoto S, Kasahara M, Egawa H, Takada Y, Kaido T, Hatano E, Nguyen JH, Chen F, Baine AM, Uemoto S. Liver transplantation for congenital biliary dilatation: a single-center experience. *Dig Surg* 2010; **27**: 492-501 [PMID: 21063126 DOI: 10.1159/000319373]
  - 25 **Fahrner R**, Dennler SGC, Dondorf F, Ardelt M, Rauchfuss F, Settmacher U. Liver resection and transplantation in Caroli disease and syndrome. *J Visc Surg* 2019; **156**: 91-95 [PMID: 29929811 DOI: 10.1016/j.jvisc Surg.2018.06.001]
  - 26 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]
  - 27 **Ammori BJ**, Jenkins BL, Lim PC, Prasad KR, Pollard SG, Lodge JP. Surgical strategy for cystic diseases of the liver in a western hepatobiliary center. *World J Surg* 2002; **26**: 462-469 [PMID: 11910481 DOI: 10.1007/s00268-001-0250-x]
  - 28 **Phinney PR**, Austin GE, Kadell BM. Cholangiocarcinoma arising in Caroli's disease. *Arch Pathol Lab Med* 1981; **105**: 194-197 [PMID: 6260057]
  - 29 **Ulrich F**, Steinmüller T, Settmacher U, Müller AR, Jonas S, Tullius SG, Neuhaus P. Therapy of Caroli's disease by orthotopic liver transplantation. *Transplant Proc* 2002; **34**: 2279-2280 [PMID: 12270398 DOI: 10.1016/s0041-1345(02)03235-9]
  - 30 **Bockhorn M**, Malagó M, Lang H, Nadalin S, Paul A, Saner F, Frilling A, Broelsch CE. The role of surgery in Caroli's disease. *J Am Coll Surg* 2006; **202**: 928-932 [PMID: 16735207 DOI: 10.1016/j.jamcollsurg.2006.02.021]
  - 31 **Ros E**, Navarro S, Bru C, Gilabert R, Bianchi L, Bruguera M. Ursodeoxycholic acid treatment of primary hepatolithiasis in Caroli's syndrome. *Lancet* 1993; **342**: 404-406 [PMID: 8101905 DOI: 10.1016/0140-6736(93)92817-d]
  - 32 **Yonem O**, Bayraktar Y. Clinical characteristics of Caroli's disease. *World J Gastroenterol* 2007; **13**: 1930-1933 [PMID: 17461492 DOI: 10.3748/wjg.v13.i13.1930]
  - 33 **Yonem O**, Bayraktar Y. Clinical characteristics of Caroli's syndrome. *World J Gastroenterol* 2007; **13**: 1934-1937 [PMID: 17461493 DOI: 10.3748/wjg.v13.i13.1934]
  - 34 **Moreno González E**, Gómez Sanz R, Hidalgo Pascual M, García García I, Rico Selas P, Calle Santiuste A, Loinaz Seguro C, Bercedo Martínez J. Surgical treatment of congenital dilatation of the biliary system. *Hepatogastroenterology* 1993; **40**: 134-138 [PMID: 8509044]
  - 35 **Tsuchida Y**, Sato T, Sanjo K, Etoh T, Hata K, Terawaki K, Suzuki I, Kawarasaki H, Idezuki Y, Nakagome Y. Evaluation of long-term results of Caroli's disease: 21 years' observation of a family with autosomal "dominant" inheritance, and review of the literature. *Hepatogastroenterology* 1995; **42**: 175-181 [PMID: 7672768]
  - 36 **Sun WB**, Han BL, Cai JX. The surgical treatment of isolated left-sided hepatolithiasis: a 22-year experience. *Surgery* 2000; **127**: 493-497 [PMID: 10819056 DOI: 10.1067/msy.2000.104663]
  - 37 **Totkas S**, Hohenberger P. Cholangiocellular carcinoma associated with segmental Caroli's disease. *Eur J Surg Oncol* 2000; **26**: 520-521 [PMID: 11016478 DOI: 10.1053/ejs.1999.0936]
  - 38 **Shimonishi T**, Sasaki M, Nakanuma Y. Precancerous lesions of intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Surg* 2000; **7**: 542-550 [PMID: 11180885 DOI: 10.1007/s005340070002]
  - 39 **Han JH**, Kim DG, Na GH, Kim EY, Lee SH, Hong TH, You YK. Evaluation of prognostic factors on recurrence after curative resections for hepatocellular carcinoma. *World J Gastroenterol* 2014; **20**: 17132-17140 [PMID: 25493027 DOI: 10.3748/wjg.v20.i45.17132]
  - 40 **Wang JH**, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. *J Hepatol* 2012; **56**: 412-418 [PMID: 21756858 DOI: 10.1016/j.jhep.2011.05.020]
  - 41 **Kluger MD**, Salceda JA, Laurent A, Tayar C, Duvoux C, Decaens T, Luciani A, Van Nhieu JT, Azoulay D, Cherqui D. Liver resection for hepatocellular carcinoma in 313 Western patients: tumor biology and underlying liver rather than tumor size drive prognosis. *J Hepatol* 2015; **62**: 1131-1140 [PMID: 25529622 DOI: 10.1016/j.jhep.2014.12.018]
  - 42 **Dondorf F**, Uteß F, Fahrner R, Felgendreß P, Ardelt M, Tautenhahn HM, Settmacher U, Rauchfuß F. Liver Transplant for Perihilar Cholangiocarcinoma (Klatskin Tumor): The Essential Role of Patient Selection. *Exp Clin Transplant* 2019; **17**: 363-369 [PMID: 29911960 DOI: 10.6002/ect.2018.0024]
  - 43 **Laurent S**, Verhelst X, Geerts A, Geboes K, De Man M, Troisi R, Vanlander A, Rogiers X, Berrevoet F, Van Vlierberghe H. Update on liver transplantation for cholangiocarcinoma: a review of the recent literature. *Acta Gastroenterol Belg* 2019; **82**: 417-420 [PMID: 31566330]
  - 44 **Yoh T**, Cauchy F, Le Roy B, Seo S, Taura K, Hobeika C, Dokmak S, Farges O, Gelli M, Sa Cunha A, Adam R, Uemoto S, Soubrane O. Prognostic value of lymphadenectomy for long-term outcomes in node-negative intrahepatic cholangiocarcinoma: A multicenter study. *Surgery* 2019; **166**: 975-982 [PMID: 31421869 DOI: 10.1016/j.surg.2019.06.025]
  - 45 **Bagante F**, Spolverato G, Merath K, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, Maithe SK, Pulitano C, Bauer TW, Shen F, Poultides GA, Soubrane O, Martel G, Koerkamp BG, Guglielmi A, Endo I, Pawlik TM. Intrahepatic cholangiocarcinoma tumor burden: A classification and regression tree model to define prognostic groups after resection. *Surgery* 2019; **166**: 983-990 [PMID: 31326191 DOI: 10.1016/j.surg.2019.06.005]
  - 46 **Lowery MA**, Goff LW, Keenan BP, Jordan E, Wang R, Bocobo AG, Chou JF, O'Reilly EM, Harding JJ, Kemeny N, Capanu M, Griffin AC, McGuire J, Venook AP, Abou-Alfa GK, Kelley RK. Second-line chemotherapy in advanced biliary cancers: A retrospective, multicenter analysis of outcomes. *Cancer* 2019; **125**: 4426-4434 [PMID: 31454426 DOI: 10.1002/encr.32463]

- 47 **Meyer CG**, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000; **69**: 1633-1637 [PMID: [10836374](#) DOI: [10.1097/00007890-200004270-00019](#)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

