Cystic duct dysplasia after cholecystectomy: a systematic review of the literature

Francesco Mongelli (✉ francesco.mongelli@mail.com)

Ospedale Regionale di Bellinzona e Valli <https://orcid.org/0000-0002-8824-651X>

Agnese Cianfarani

Ospedale Regionale di Bellinzona e Valli

Matteo Di Giuseppe

Ospedale Regionale di Bellinzona e Valli

Antonjaco Ferrario Di Tor Vajana

Ospedale Regionale di Bellinzona e Valli

Andrea Saporito

Ospedale Regionale di Bellinzona e Valli

Fabio Garofalo

Ospedale Regionale di Lugano Civico e Italiano

Davide La Regina

Ospedale Regionale di Bellinzona e Valli

Research article

Keywords: gallstone, cystic duct, cystic stump, dysplasia, cholecystectomy

Posted Date: July 9th, 2019

DOI: <https://doi.org/10.21203/rs.2.11161/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at International Surgery Journal on October 24th, 2019. See the published version at <https://doi.org/10.18203/2349-2902.isj20195155>.

Abstract

Purpose Approximately 1 to 3.5% of cholecystectomies are found to have incidental dysplasia on histological examination. Cases of positive resection margins on the cystic stump are rare and evidence lack. The aim of this article was to systematically review the literature and to suggest a possible management algorithm. **Methods** We searched PubMed, Cochrane Library and Google Scholar databases by combining “cholecystectomy” AND “dysplasia” AND “cystic” according to PRISMA guidelines. Studies providing information about cystic duct dysplasia with positive resection margin after cholecystectomy were included. **Results** The searches identified 109 articles from PubMed and 4 articles from Cochrane Library and Google Scholar, of which three were eligible. Five were found to have post-operative high-grade dysplasia, one patient had a carcinoma and one had a low-grade dysplasia. Median follow-up was of 10.5 months (range: 0.5 – 26.6 months), no evidence of recurrence was found in patients with dysplasia, while the patient with diagnosis of cholangiocarcinoma died during follow-up. **Conclusions** Patients with positive resection margins for dysplasia after cholecystectomy should be considered for a surgical treatment. The latter depends on several factors related to the patient and the grade of dysplasia itself. Simple cystic duct stump excision has been suggested and it seems to be safe and effective with no evidence of recurrence during follow-up when a R0 resection is achieved. A multidisciplinary approach and a surveillance program should be always taken into account.

Background

Gallstone disease is an extremely widespread disease, being the estimated prevalence around 10-15% in adult population. Symptoms leading to cholecystectomy can be identified in up to 35% of patients with cholelithiasis [1], making the laparoscopic cholecystectomy one of the most commonly performed surgical operations in developed countries [2].

Approximately 1 to 3.5% of cholecystectomies are found to have incidental dysplasia on histological examination [3-5]. Biliary dysplasia is considered a risk factor for the development of an invasive carcinoma [6]. Usually, dysplasia does not reach the resection margin, so that no further treatment is needed after cholecystectomy [7]. The clinical implications and management of the resection margin involvement by dysplastic changes are unknown.

In this article, we discuss this matter and suggest a possible management algorithm.

Methods

Search strategy

Two researchers independently searched the PubMed, Cochrane Library and Google Scholar databases by combining “cholecystectomy” AND “dysplasia” AND “cystic” (last update: June 1 2019) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8].

Inclusion and exclusion criteria

Were included studies providing adequate information about the cystic duct or stump dysplasia after cholecystectomy on the histopathological examination. Studies were excluded in case of a proved diagnosis of gallbladder or cystic duct cancer.

Study selection and quality assessment

Two reviewers independently evaluated titles and abstracts to choose potential studies. If data were duplicated or overlapping, only the most recent data were included. Studies not matching inclusion and exclusion criteria were discarded. Studies potentially suitable for inclusion were evaluated in full-text. Disagreements were resolved by discussion. The evidence quality of was assessed with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE approach) [9]. In particular, it was rated from 4 to 1, corresponding 4 to a high level of evidence, 3 to moderate, 2 to low and 1 to very low. With this methodology, the risk of bias, inconsistency, indirectness, imprecision and publication bias were considered to possibly reduce the quality of evidence by 1 or 2 points according to the importance of the factor itself.

Results

The searches identified 109 articles from PubMed and 4 articles from Cochrane Library and Google Scholar. After removing duplicates, 110 studies remained. Abstracts and titles were screened and 12 articles were considered potentially eligible. Full texts of these studies were retrieved and analysed. Nine studies were excluded because did not match inclusion and exclusion criteria. Finally, three studies were found eligible and considered in this systematic review [10-12] (Figure 1). The characteristics of the included studies are given in Table 1.

Seven patients were found in the medical literature. Median age at the moment of the diagnosis was 61 years old (range: 36 – 77). Pre-operative radiographic abnormalities were detected only in 2 out of 7 patients. Four patients had simple cystic duct resection with one 1 case of bile duct exploration for gallstone, 1 patient had cystic duct resection with lymphadenectomy and IV and V segments hepatectomy, 2 patients had bile duct resection with lymphadenectomy , in 1 case with associated IV and V segments hepatectomy. Five patients were found to have post-operative high-grade dysplasia, one patient had a carcinoma and one had a low-grade dysplasia. Median follow-up was of 10.5 months (range: 0.5 – 26.6 months), no evidence of recurrence was found in patients with dysplasia. The patient with pathological diagnosis of cholangiocarcinoma died during follow-up after 15.3 months after surgery. Based on these considerations the proposal for a therapeutic algorithm is presented in figure 2.

According to the GRADE approach, due to sparse data and other limitations in the quality of selected studies, the overall quality of evidence of this systematic review was judged “very low” (level of evidence 5).

Discussion

Cancers of the biliary tract could involve the intra- and extrahepatic ducts, gallbladder and ampulla [13]. The involved biliary segment has been described to vary among different countries, being the intrahepatic carcinoma more common in Asia and the gallbladder cancer in South America. Gallstones are the most important risk factor for the development of a gallbladder cancer and in 70-90% of cases of gallbladder cancer gallstones can be identified [14]. Chronic inflammation, Caroli's disease, choledochal cysts, infectious diseases as well as a variety of biological and chemical toxins are further factors associated with biliary cancer development [14]. The carcinogenesis of biliary neoplasm is thought to be a multi-step process from metaplasia to malignant degeneration. Antral metaplasia, hyperplasia, non-neoplastic polyps represent non-neoplastic lesions and can be found in around 9 - 59.5% of cases after cholecystectomy [15,16]. The bile-type epithelium with columnar cells and round to oval uniform nuclei differ from the dysplastic changes that are characterized by the loss of epithelium architecture, increased height of cells and nuclear crowding with presence of mitotic figures (figure 3). While reactive changes blend gradually with the normal cells' architecture, real dysplasia has sharp demarcated areas adjacent to the normal biliary epithelium [6].

Depending on the severity of atypia, dysplasia can be defined as either low- or high-grade. Terms like “moderate” or “severe” dysplasia, as well as “carcinoma in situ” are used to describe histological changes of biliary epithelium. Zen et al. [17] described two main types of premalignant dysplastic lesions: the biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasms (IPN-B). The latter is considered less common, it is associated with ectasia of extrahepatic biliary ducts and cysts formation with an exophytic proliferation of biliary epithelium. Moreover, it can be associated with abdominal pain and jaundice.

Zen et al. [17] originally described BilIN as microscopic alterations, asymptomatic and not appreciable with imaging studies. BilIN is frequently detectable in specimens with invasive carcinoma and is an incidental finding in 1% to 3.5% of cholecystectomies. BilIN was recently classified by the World Hospital Organization according to the degree of atypia in BilIN1, BilIN2 and BilIN3 [18]. Therefore, BilIN1 corresponds to low-grade, BilIN2 to intermediate grade and BilIN3 to a high-grade of dysplasia. Although this grading-system may be useful, in daily practice it is easier to apply a two-tiered system (low-grade and high-grade dysplasia).

The 5-year survival rate of patients with cholangiocarcinoma is thought to be around 5%-10%. An improved overall survival can only be achieved through a complete surgical resection with tumour-free margins [19] but, unfortunately, these surgical results are difficult to achieve as frequently an advanced disease is diagnosed [20]. Mizumoto et al. [21] reported a 5-year survival rate

for early bile duct cancer of 100%. Kurosaki et al. [22] reported a 5-year survival rate for 7 patients with pT1 bile duct cancer of 86%. Therefore, in case of biliary dysplasia, strategies involving prophylactic surgical resections or detection of cancers at early stage could have a dramatic impact on patient's prognosis.

Bickenbach et al. [10] reported a series of five patients with high-grade dysplasia at the cystic duct margin after cholecystectomy without preoperative evidence of malignancy. One of the five patients was found to have a carcinoma and deceased after 15 months despite proper surgery and adjuvant chemotherapy. From this small series, the authors concluded that the risk of underlying bile duct cancer in case of high-grade dysplasia at the cystic stump is not neglectable, as about 10% of biliary carcinomas are multifocal. So, high-grade dysplasia of the cystic stump could represent multifocal neoplastic changes of biliary ducts or express a wide extension of an underlying malignancy. In a recent case report, Moslim et al. [11] suggested the surgical intervention with excision and reconstruction of the main duct in case of positive cystic duct resection margins. More recently, Cianfarani et al. [12] reported a case of positive resection margins for low-grade dysplasia on the cystic duct that was successfully surgical treated with a cystic stump resection.

The lack of literature about the surveillance of cystic duct dysplasia makes difficult to draw conclusions. A possible management algorithm is shown in figure 2. Due to the known progression to carcinoma and the multifocality, a multidisciplinary board evaluation in case of dysplasia of the cystic duct is strongly advisable. The surgical treatment of positive resection margins after cholecystectomy with high-grade dysplasia should be considered mandatory. The treatment of cases with low-grade dysplasia should be tailored on patient's age and general conditions, but a surgical resection can be a reasonable option. Due to the high rate of dysplasia multifocality, an optimal surveillance program should be considered in patient with low- and high-grade dysplasia. There is no evidence that supports one or the other method, so that its choice should be based on the local experience and resources. MRCP, ERCP with SpyGlass cholangioscopy, echoendoscopy and regular liver function tests can play a role in surveillance programs.

The main limitation of our study is the sparse data available in literature on positive resection margins for dysplasia after cholecystectomy. A case series and two case reports make difficult to draw proper conclusions. Nevertheless, literature on the gallbladder and the biliary tree dysplasia provides sufficient data to propose a possible treatment algorithm for this uncommon condition.

Conclusions

Patients with positive resection margins for dysplasia after cholecystectomy should be considered for a surgical treatment. The latter depends on several factors related to the patient and the grade of dysplasia itself. Simple cystic duct stump excision has been suggested and it seems to be safe and effective with no evidence of recurrence during follow-up when a R0 resection is achieved. A multidisciplinary approach and a surveillance program should be always taken into account. Our possible management algorithm of this uncommon disease needs to be validated and should be the matter of future studies.

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses. MRCP: Magnetic Resonance Cholangiopancreatography. ERCP: Endoscopic Retrograde Cholangiopancreatography. BillIN: Biliary intraepithelial neoplasia. IPN-B: intraductal papillary neoplasms. GRADE: Grading of Recommendations, Assessment, Development and Evaluations.

Declarations

- **Ethics approval and consent to participate:** this study was cleared with the institution review board (IRB) with positive result. Documentation is available on request to the corresponding author.
- **Consent for publication:** not applicable.
- **Availability of data and materials:** The dataset used and/or analysed during the current study is available from the corresponding author on reasonable request.

- **Competing interests:** The authors declare that they have no competing interests.
- **Funding:** The authors report no grant or financial support.
- **Authors' contributions:** Protocol/project development: FM, AC, MDG, AFTV. Data acquisition and interpretation of data: FM, DLR, AS, FG, MDG. Statistics analysis of data: AC, AS. Manuscript drafting: DLR, FM, AS, AC, FG. Manuscript Revision and accountable for all aspects of the work: FM, AC, MDG, AFTV AS, FG, DLR. All authors read and approved the final manuscript.
- **Acknowledgements:**

References

1. Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. *J Long Term Eff Med Implants*. 2005;15:329-38.
2. Gurusamy KS, Davidson BR. Gallstones. *BMJ* 2014; 348:g2669.
3. Talreja V, Ali A, Khawaja R, Rani K, Samnani SS, Farid FN. Surgically Resected Gall Bladder: Is Histopathology Needed for All? *Surg Res Pract*. 2016;2016:9319147.
4. Roa I, Ibacache G, Muñoz S, de Aretxabala X. Gallbladder cancer in Chile: Pathologic characteristics of survival and prognostic factors: analysis of 1,366 cases. *Am J Clin Pathol*. 2014;141:675-82.
5. Wrenn SM, Callas PW, Abu-Jaish W. Histopathological examination of specimen following cholecystectomy: Are we accepting resect and discard? *Surg Endosc*. 2017;31:586-93.
6. Katabi N. Neoplasia of gallbladder and biliary epithelium. *Arch Pathol Lab Med*. 2010;134:1621–7.
7. Rais R, González I, Chatterjee D. Dysplasia in Gallbladder: What Should We Do? *J Gastrointest Surg*. 2019;23:686-9.
8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
9. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401-6.
10. Bickenbach KA, Shia J, Klimstra DS, DeMatteo RP, Fong Y, Kingham TP et al. High-grade dysplasia of the cystic duct margin in the absence of malignancy after cholecystectomy. *HPB (Oxford)*. 2011;13:865-8.
11. Moslim MA, Tang A, Morris-Stiff G. Management of high-grade dysplasia of the cystic duct after cholecystectomy. *BMJ Case Rep*. 2017;2017.
12. Cianfarani A, Mongelli F, Di Giuseppe M, La Regina D. Dysplasia of Cystic Duct and Positive Resection Margins after Cholecystectomy: A Challenging Decision Making Process. *J Surg* 2019;4:1195.
13. Klöppel G, Adsay V, Konukiewitz B, Kleeff J, Schlitter AM, Esposito I. Precancerous lesions of the biliary tree. *Best Pract Res Clin Gastroenterol*. 2013;27:285-97.
14. Marcano-Bonilla L, Mohamed EA, Mounajjed T, Roberts LR. Biliary tract cancers: epidemiology, molecular pathogenesis and genetic risk associations. *Chin Clin Oncol*. 2016;5:61.
15. Esendağlı G, Akarca FG, Balcı S, Argon A, Erhan SŞ, Turhan N et al. A Retrospective Evaluation of the Epithelial Changes/Lesions and Neoplasms of the Gallbladder in Turkey and a Review of the Existing Sampling Methods: A Multicentre Study. *Turk Patoloji Derg*. 2018;34:41-8.
16. Mukhopadhyay S, Landas SK. Putative precursors of gallbladder dysplasia: a review of 400 routinely resected specimens. *Arch Pathol Lab Med*. 2005;129:386–90.
17. Zen Y, Aishima S, Ajioka Y, Haratake J, Kage M, Kondo F et al. Proposal of histological criteria for intraepithelial atypical/proliferative biliary epithelial lesions of the bile duct in hepatolithiasis with respect to cholangiocarcinoma: preliminary report based on interobserver agreement. *Pathol Int*. 2005;55:180-8.
18. Akiba J, Nakashima O, Hattori S, Tanikawa K, Takenaka M, Nakayama M et al. Clinicopathologic analysis of combined hepatocellular-cholangiocarcinoma according to the latest WHO classification. *Am J Surg Pathol*. 2013;37:496-505.

19. Cillo U, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt HJ et al. Surgery For Cholangiocarcinoma. Liver Int. 2019. Epub ahead of print.

20. Cha JM, Kim MH, Jang SJ. Early bile duct cancer. World J Gastroenterol. 2007;13:3409-16.

21. Mizumoto R, Ogura Y, Kusuda T. Definition and diagnosis of early cancer of the biliary tract. Hepatogastroenterology. 1993 Feb;40:69-77.

22. Kurosaki I, Tsukada K, Watanabe H, Hatakeyama K. Prognostic determinants in extrahepatic bile duct cancer. Hepatogastroenterology. 1998;45:905-9.

Tables

Table 1: Patient characteristics of included studies

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Male	Female	Male	Male	Female	Female	Female
Age (years)	66	77	61	65	57	36	44
Preoperative imaging	MRCP	PET/CT	MRCP	CT MARCP	MRCP ERCP	CT MRCP ERCP	No preoperative images
Preoperative pathology	High-grade dysplasia	High-grade dysplasia	High-grade dysplasia	High-grade dysplasia	High-grade dysplasia	High-grade dysplasia	Low-grade dysplasia
Radiographic abnormality	Mildly dilated cystic duct stump Borderline enlarged lymph node	No suspicious findings	No suspicious findings	Minimal thickening of cystic stump Small lesions in segments III and IV of the liver	No suspicious findings	No suspicious findings	-
Operation	Bile duct resection, portal lymphadenectomy, partial hepatectomy segments IV and V	Cystic duct excision, portal Lymphadenectomy, partial hepatectomy segments IV and V	Cystic duct excision, common bile duct exploration with removal of stone	Bile duct resection and portal lymphadenectomy	Cystic duct resection	Cystic duct resection	Cystic duct resection
Operative findings	Palpable mass at cystic duct remnant, enlarged portal lymph nodes	None	Common bile duct stones	Palpable mass at cystic duct remnant No liver lesions identified	None	None	None
Pathology	Cholangiocarcinoma (T2N1) 4/6 nodes positive	No evidence of malignancy or dysplasia	No evidence of malignancy or dysplasia	No evidence of malignancy or dysplasia	No evidence of malignancy or dysplasia	No evidence of malignancy or dysplasia	No evidence of malignancy or dysplasia
Status	Deceased during follow-up after 15.3 months	No evidence of disease after 0.9 months	No evidence of disease after 16.0 months	No evidence of disease after 25.6 months	No evidence of disease after 2.1 months	No evidence of disease after 0.5 months	Not reported

MRCP, magnetic resonance cholangiopancreatography; PET, positron emission tomography; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography;

CBD, common bile duct.

Figures

Figure 1

Possible therapeutic algorithm for the treatment of cystic duct dysplasia with positive resection margins.

Figure 2

Flow chart of the literature search according to PRISMA Guidelines.

Figure 3

Histologic exam showing a low-grade dysplasia on the cystic duct stump.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMANMAchecklist.docx](#)