RESEARCH ARTICLE

Does additional resection of a positive microscopic ductal margin benefit patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis

Qiao Ke1*, Yuqing Chen2*, Qizhen Huang3*, Nanping Lin3*, Lei Wang3,4*, Jingfeng Liu1

1 Department of Hepatopancreatobiliary Surgery, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, Fujian, China, 2 The Graduate School of Fujian Medical University, Fuzhou, Fujian, China, 3 Department of Radiation Oncology, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, Fujian, China, 4 Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, China

* These authors contributed equally to this work.
** wangley001@126.com

Abstract

Background

The incidence of a positive microscopic ductal margin (R1) after surgical resection for perihilar cholangiocarcinoma (pCCA) remains high, but the beneficial of additional resection has not been confirmed by any meta-analysis and randomized clinical trials (RCT), which also increased the risk of morbidity and mortality. Hence, a systematic review is warranted to evaluate the clinical value of additional resection of intraoperative R1 for pCCA.

Methods

Eligible studies were searched by PubMed, MedLine, Embase, the Cochrane Library, Web of Science, from Jan.1st 2000 to Nov.30th 2019, evaluating the 1-, 3-, and 5-year overall survival (OS) rates of additional resection of intraoperative pathologic R1 for pCCA. Odds ratio (OR) with 95% confidence interval (CI) was used to determine the effect size by a randomized-effect model.

Results

Eight studies were enrolled in this meta-analysis, including 179 patients in the secondary R0 group, 843 patients in the primary R0 group and 253 patients in the R1 group. The pooled OR for the 1-, 3-, and 5-year OS rate between secondary R0 group and primary R0 group were 1.03(95%CI 0.64~1.67, P = 0.90), 0.92(95%CI 0.52~1.64, P = 0.78), and 0.83(95%CI 0.37~1.84, P = 0.65), respectively. The pooled OR for the 1-, 3-, and 5-year OS rate between secondary R0 group and R1 group were 2.14(95%CI 1.31~3.50, P = 0.002), 2.58 (95%CI 1.28~5.21, P = 0.008), and 3.54(95%CI 1.67~7.50, P = 0.001), respectively. However, subgroup analysis of the West showed that the pooled OR for the 1-, and 3-year OS
rate between secondary R0 group and R1 group were 2.05 (95% CI 0.95–4.41, P = 0.07), 1.91 (95% CI 0.96–3.81, P = 0.07), respectively.

Conclusion
With the current data, additional resection should be recommended in selected patients with intraoperative R1, but the conclusion is needed further validation.

Introduction
The incidence of perihilar cholangiocarcinoma (pCCA) is increasing stably [1], but the prognosis is generally poor [2, 3]. Surgical resection is the only potential way to achieve a long survival [3, 4], although only 20% patients are operable at diagnosis [5, 6]. However, the 5-year survival rates were reported to be 15–40% [7–9], and the incidence of recurrence within two years was reported to be as high as 80% [10]. Positive bile duct margin is one of the most important factors for poor prognosis of pCCA after resection [11–13], and the incidence of a positive microscopic ductal margin (R1) ranged from 10–72% [11, 13, 14]. Hence, additional resection is necessary to achieve a margin-negative (R0) resection and improved prognosis once R1 was confirmed by intraoperative frozen pathology.

However, additional resection of pCCA typically increased the risk of perioperative morbidity and mortality [14–16]. In addition, secondary R0 resection is hard to achieve in selected patients with more advanced disease and concurrent major vascular invasion [17, 18]. What’s more, it remains controversial whether patients with pCCA could be benefited from additional resection [13, 14, 17, 19], and to the best of our knowledge, no meta-analysis or randomized clinical trials (RCT) have been published on this issue. Hence, a meta-analysis was warranted to evaluate the clinical value of additional resection of intraoperative R1 for pCCA.

Material and method
This study was based on published studies and the informed consent of the patients and the ethical approval were not required. This meta-analysis was conducted according to the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Literature search
A comprehensive search on the existing published medical literature was conducted by two independent researchers to investigate the outcomes of additional resection of intraoperative R1 for pCCA. English electronic databases such as PubMed, MedLine, Embase, the Cochrane Library, Web of Science were used to search the literature from Jan. 1st 2000 to Nov. 30th 2019. Key words were as follows: (“hilar cholangiocarcinoma” or “perihilar cholangiocarcinoma” or “Klatskin’s tumor” or “HCCA” or “pCCA”) AND (“additional resection” or “extensive resection” or “re-resection”) AND (“margin”). The references of the included studies, relevant meta-analyses, reviews and guidelines were manually screened to look for potentially eligible studies.

Selection criteria
Inclusion criteria: i) patients with pCCA; ii) additional resection were conducted once R1 was confirmed by intraoperative frozen pathology; iii) comparison between secondary R0 and
primary R0 or R1; iv) outcomes including overall survival (OS) rate; v) either randomized controlled trial (RCT) or retrospective studies.

Exclusion criteria: i) patients including non-pCCA; ii) data on the OS rates was not available; iii) grouping information was blur; ) studies based on overlapping cohorts deriving from the same center.

**Intervention**

Hepatectomy with en-bloc total caudate lobe resection, and regional lymphadenectomy along with (+/-) vascular resection and reconstruction was conducted as a standard procedure for pCCA [4, 20], but the detailed procedure was different from each center [4, 20].

Both distal bile duct margin (DM) and proximal bile duct margin (PM) were collected to conduct an intraoperative frozen-section examination, and were evaluated by at least two pathologists within 30 min [21]. Of note, R1 was defined as microscopical positive ductal margin, including invasive carcinoma (R-inv) and carcinoma in situ (R-cis) [19].

Additional resection was performed when either DM or PM was positive. Additional resection typically involved extended hepatectomy and/or extirpation of the biliary tree, but the detailed procedure was different from each center [13, 14, 17, 18].

**Data extraction**

Data such as the author’s first name, year of publication, study methods, patient’s characteristic, interventions, and outcomes were extracted and assessed by two independent investigators with predefined forms such as baseline characteristics and outcomes from each study. The odd ratios (ORs) of 1-, 3-, and 5-year OS were extracted directly from the original data or extracted from the Kaplan-Meier curves according to the methods described in detail by Tierney et al [22], and Parmar et al [23]. In case of disagreement, a third investigator intervened for a conclusion.

**Quality assessment**

The quality of non-randomized studies was assessed by the modified Newcastle-Ottawa Scale (NOS) [24], and more than 7 stars were defined as high quality, 4–6 star as medium quality, and <4 stars as low quality.

**Statistical analysis**

The meta-analysis was registered at http://www.crd.york.ac.uk/PROSPERO/ (Review registry 133971) and was performed using RevMan Version 5.3. ORs and 95%CIs were used to evaluate the 1-, 3-, and 5-year OS rates between secondary R0 and primary R0 or R1. Considering the inherent heterogeneity among the included studies, the pooled ORs for 1-, 3-, and 5-year OS rates were evaluated by the random-effects model [25]. But in the subgroup analysis, to choose whether random-effects or fixed-effects model was determined by heterogeneity test. The heterogeneity was assessed by the $\chi^2$ test and $I^2$ statistics; $P < 0.10$ or $I^2 > 50\%$ were considered as significant heterogeneity. When the hypothesis of homogeneity was rejected, the fixed-effects model was used to estimate the case with homogeneity, and the random-effects model was used for the cases with significant heterogeneity [26]. Sensitivity analysis was conducted as follows: one study at a time was removed and the remained were re-analyzed to determine whether the results could be affected significantly by single study [27]. Begg’s and Egger’s tests were used to evaluate publication bias using Stata 14.
Results

Base characteristic of the included studies

Initially, 388 records were identified by two independent reviewers. A total of 15 records were excluded after duplicate removal by NoteExpress 3.1. After browsing titles and abstracts, 29 records remained. And then, 19 records were excluded after full text review for the following reasons: i) two records for patients not pCCA [28, 29]; iii) 14 records for unclear grouping; ii) three records for data unavailable [21, 30, 31]. Among the remaining 10 records, one was excluded for letter [3, 32], and one for systematic review [3]. Finally, eight reports were enrolled for analysis [13, 14, 17–19, 33–35], and all of them were non-RCTs. In total, 1275 patients were enrolled in this meta-analysis, including 179 patients in the secondary R0 group, 843 patients in the primary R0 group and 253 patients in the R1 group. The search strategies and results were shown in Fig 1.

The characteristics and baseline demographic data of the patients in each research were listed in Table 1, and the surgical procedure of additional resection were depicted in Table 2.

Methodological quality of the included studies

The quality of each included research was shown in Table 1. Seven researches were assessed be of high quality [13, 14, 17–19, 34, 35], and one were of medium quality [33].

Primary endpoint

The 1-, 3-, and 5-year OS rates comparing between secondary R0 group and primary R0 group were evaluated in six included studies [13, 14, 17, 19, 34, 35]. The pooled OR for the 1-, 3-, and 5-year OS rate between secondary R0 group and primary R0 group were 1.03 (95% CI 0.64–1.67, P = 0.90, Fig 2A), 0.92 (95% CI 0.52–1.64, P = 0.78, Fig 2B), and 0.83 (95% CI 0.37–1.84, P = 0.65, Fig 2C), respectively.

The 1-, 3-, and 5-year OS rates comparing between secondary R0 group and R1 group were evaluated in eight included studies [13, 14, 17–19, 33–35]. The pooled OR for the 1-, 3-, and 5-year OS rate between secondary R0 group and R1 group were 2.14 (95% CI 1.31–3.50, P = 0.002, Fig 3A), 2.58 (95% CI 1.28–5.21, P = 0.008, Fig 3B), and 3.54 (95% CI 1.67–7.50, P = 0.001, Fig 3C), respectively.

Subgroup analysis stratified by the West and the East

A total of three researches from the West were included in this meta-analysis [14, 19, 34], including two from the USA [19, 34] and one from Italy [14]. The pooled OR for the 1-, and 3-year OS rate between secondary R0 group and primary R0 group were 1.19 (95% CI 0.58–2.44, P = 0.64, Table 3), 1.00 (95% CI 0.57–1.78, P = 0.99, Table 3), respectively. And, the pooled OR for the 1-, and 3-year OS rate between secondary R0 group and R1 group were 2.05 (95% CI 0.95–4.41, P = 0.07, Table 3), 1.91 (95% CI 0.96–3.81, P = 0.07, Table 3), respectively.

A total of five researches from the East were included in this meta-analysis [13, 17, 18, 33, 35], including three from Japan [13, 18, 35], one from South Korea [33], and one from China [17]. The pooled OR for the 1-, and 3-year OS rate between secondary R0 group and primary R0 group were 0.94 (95% CI 0.43–2.02, P = 0.87, Table 3), 0.66 (95% CI 0.38–1.16, P = 0.15, Table 3), respectively. And, the pooled OR for the 1-, and 3-year OS rate between secondary R0 group and R1 group were 2.19 (95% CI 1.18–4.07, P = 0.01, Table 3), 3.21 (95% CI 1.75–5.89, P < 0.001, Table 3), respectively.
Prognostic factors for pCCA after resection

Prognostic factors were analyzed in six studies using univariate and multivariate analysis [13, 17, 19, 33–35]. Tumor differentiation, lymph node involvement, combined PV and/or HA, microscopic venous invasion, microscopic liver invasion, and tumor stage were confirmed to be independent risk factors of overall survival. Details were depicted in Table 4.
Sensitivity analysis and publication bias

Removal of any individual study did not affect the overall outcome of this meta-analysis significantly in the sensitivity analysis. Significant publication bias was not observed in the pooled OR for 1-, 3-, and 5-year OS between secondary R0 and primary R0/R1 (all P > 0.05, Fig 4).

Discussion

This was the first meta-analysis that evaluated the clinical value of additional resection of intraoperative R1 for pCCA. A total of 8 studies with 1275 patients were included in this meta-analysis. Results showed that the 1-, 3-, and 5-year OS rates were comparable between patients with secondary R0 and patients with primary R0, but both are better than patients with R1.
Hence, additional resection for pCCA was recommended in case of intraoperative R1 to achieve a better prognosis, especially in selected patients.

R0 resection is a standard procedure for curative pCCA, although the detailed procedures are different from each other worldwide [4, 36–38]. But the incidence of R1 was as high as 10–72% [11, 13, 14], mainly due to the complex anatomy of hepatic hilar and biological characteristics of pCCA. And, patients with R1 had a poor prognosis [11–13]. In this meta-analysis, the initial R1 ranged from 12.3% to 37.2%. Hence, additional resection of intraoperative pathologic R1 for pCCA is necessary to achieve a better prognosis. However, it remains controversial whether additional resection could benefit the patients with intraoperative R1 in the view of long-term prognosis [13, 14, 17, 19]. In this meta-analysis, we found that the 1-, 3-, and 5-year OS rates in the secondary R0 group were higher than those in the R1 group, but the median survival time (MST) in the primary R0, secondary R0, and R1 were 22.3–56.6 months, 20.99–38 months, and 11.60–32 months, respectively. Hence, the conclusion that patients with intraoperative pathologic R1 would be benefited from additional resection needed further validation.

However, not all patients with intraoperative R1 would be benefited from resection. Major differences were found in patient characteristics and treatment strategies between the East and the West pCCA cohorts [39]. In the subgroup of the West, there were no significant difference in the pooled OR for the 1- and 3- year OS of patients between secondary R0 group and R1 group, which suggested that additional resection would not benefit patients in the West. Reasons might be as follows: 1) epidemiology of pCCA was greatly different between the West and East, the incidence of pCCA was much higher in the East than that in the West [40]. What’s more, liver fluke was the leading etiology of pCCA in the East while it was primary sclerosing cholangitis in the West [40]; 2) cirrhosis was an important factor of decision-making on hepatectomy, which was much more frequent and serious in the East [39]; 3) pCCA patients were typically present with obstructive jaundice, and endoscopic biliary drainage was found to be associated with improved prognosis compared with percutaneous biliary drainage, which was conducted much more frequently in the East [41]; 4) preoperative portal vein embolization was repeatedly confirmed to be able to improve the prognosis of pCCA via increasing the future remnant liver volume, which was also performed much often in the East [42, 43]; 4)

Table 2. Surgical procedures of included studies.

| Study                  | Endo 2008 [34] | Shingu 2010 [35] | Ribero 2011 [14] | Lee 2012 [33] | Oguro 2015 [13] | Ma 2018 [17] | Zhang 2018 [19] | Otsuka 2019 [18] |
|------------------------|----------------|-----------------|-----------------|-------------|---------------|-------------|---------------|----------------|
| Bile duct resection only | NA             | 15              | 7               | 30          | NA            | NA          | 56            | 44            |
| Left hepatectomy       | 83             | 107             | 30              | 27          | 97            | 120         | 63            | 21            |
| Left trisectionectomy  | 43             | 3               | 13              | 25          | 7             | 37          | 9             | 9             |
| Mesohepatectomy        | 6              | 1               | 3               | 2           | 9             | NA          | NA            | NA            |
| Right hepatectomy      | 100            | 13              | 65              | 95          | 49            | 34          | 33            | 33            |
| Right trisectionectomy | 12             | 26              | 19              | 5           | 13            | 64          | 8             | 8             |
| Other hepatectomies    | 20             | 2               | 13              | NA          | NA            | NA          | NA            | NA            |
| Combined caudate lobe resection | 36        | 268             | NA              | NA          | NA            | NA          | 90            | NA            |
| Combined pancreatoduodenectomy | NA  | 28             | 2               | 3           | 13            | NA          | 3             | 9             |
| Combined portal vein resection | 9        | 87              | 20              | 9           | 46            | 57          | NA            | 20            |
| Combined hepatic artery resection | NR  | 22             | 2               | 3           | 21            | 32          | NA            | 7             |

NA, not available.

https://doi.org/10.1371/journal.pone.0232590.t002
surgical techniques including vascular reconstruction, and lymph node dissection have been conducted prevalently in Japan, South Korea, and China without increased risk of severe postoperative complications [39].

In an attempt to achieve a secondary R0, more extensive resection would be proposed, which would increase the risk of morbidity and mortality in turn. Liver failure, biliary fistula, anastomotic leak, surgical site infection, intra-abdominal bleeding, and vascular complications are the common complications related to additional resection, and the morbidity ranged from 40~71.2% [19, 44]. The procedure related postoperative mortality varied from 2 to 15% [45, 46], although it was reported to be decreased [9]. Additional resection should better be conducted in highly experienced centers if future remnant liver volume was adequate and additional resection was feasible in anatomy, but data on morbidity and mortality was unavailable in most of the included studies. In addition, considering that the longitudinal infiltration of

![Fig 2. Forest plot of overall survival rates between secondary R0 group and primary R0 group.](https://doi.org/10.1371/journal.pone.0232590.g002)
pCCA along the bile duct was confirmed to be 4.6mm~14.0mm [47], minor additional resection was recommended in case of intraoperative R1, on condition that a secondary R0 was guaranteed.

As is known to all, one size does not fit for all. R1 typical includes R-inv and R-cis, and R-inv is much more aggressive than R-cis in pathology theoretically [3, 29]. However, recent studies showed that addition resection could not improve the prognosis of extrahepatic
cholangiocarcinoma patients with initial R-cis [18, 48]. In our newly published meta-analysis, no significant differences were observed in the 1-, 2-, and 3-year survival rates between groups of R0 and R-cis (all $P > 0.05$), both of which were significantly higher than those in the group of R-inv (all $P < 0.05$) [49], which indicated that additional resection would be not necessary for patients with initial R-cis. Unfortunately, relevant data was unable to extract in the included studies, and further studies are badly needed on this issue.

Intraoperative frozen section analysis is prevalently used to assess resection margins during cancer surgery, and is a determinant whether addition resection is warranted to achieve R0 [50, 51]. But the clinical value of intraoperative frozen section in pCCA was limited, because the sensitivity was reported to be only 68% [21]. The inconsistency between frozen section and permanent histopathological analyses of bile ductal margin might be explained by as follows: 1) the biological characteristics of pCCA, because pCCA often spread longitudinally along the axis of the bile duct, partially in the submucosal space with wide invasion to the perilymph, perineural and perivasculature [52], which increased the risk of sampling errors; 2) the presence of atypical cells within the boundary zone between the tumor and the normal duct epithelium [34]; 3) unrecognized margin due to energy surgical instruments such as CUSA, Endo-GIA and so on. However, intraoperative R1 could put the surgeons into a dilemma because

| Subgroup                          | Studies included | Overall Survival |   |
|----------------------------------|------------------|-----------------|---|
|                                  | Participants     | Effect model    | OR(95%CI) |   |
| The West, Secondary R0 vs. Primary R0 |                  |                |            |   |
| 1-year                           | 3                | Fixed           | 1.19(0.58–2.44) | 0.64 |
| 3-year                           | 3                | Fixed           | 1.00(0.57–1.78) | 0.99 |
| The East, Secondary R0 vs. Primary R0 |                  |                |            |   |
| 1-year                           | 5                | Fixed           | 0.94(0.43–2.02) | 0.87 |
| 3-year                           | 5                | Random          | 0.66(0.38–1.16) | 0.15 |
| The West, Secondary R0 vs. R1     |                  |                |            |   |
| 1-year                           | 3                | Fixed           | 2.05(0.95–4.41) | 0.07 |
| 3-year                           | 3                | Fixed           | 1.91(0.96–3.81) | 0.07 |
| The East, Secondary R0 vs. R1     |                  |                |            |   |
| 1-year                           | 5                | Fixed           | 2.19(1.18–4.07) | 0.01 |
| 3-year                           | 5                | Fixed           | 3.21(1.75–5.89) | <0.001 |

https://doi.org/10.1371/journal.pone.0232590.t003

| Prognostic factors                          | Studies included | Heterogeneity | Hazard ratio | 95%CI   |
|---------------------------------------------|------------------|---------------|--------------|---------|
| Tumour differentiation (others versus well differentiated) | 6                | 0             | 2.25         | 1.82–2.79 |
| Lymph node involvement (yes versus no)      | 6                | 0             | 1.85         | 1.55–2.21 |
| Combined PV and/or HA (yes versus no)       | 3                | 37            | 1.37         | 1.11–1.69 |
| Microscopic perineural invasion (yes versus no) | 3                | 66            | 1.59         | 0.94–2.68 |
| Microscopic venous invasion (yes versus no)  | 2                | 0             | 1.42         | 1.08–1.86 |
| Microscopic liver invasion (yes versus no)   | 2                | 0             | 1.43         | 1.08–1.90 |
| Tumour status (T3+T4 versus T1+T2)*         | 2                | 0             | 1.23         | 1.02–1.46 |

PA, portal vein resection; HA, hepatic artery resection;
*according to the 8th edition American Joint Committee on Cancer (AJCC) staging guidelines.

https://doi.org/10.1371/journal.pone.0232590.t004
Additional resection increased the risk of morbidity or was sometimes impossible anatomically.

There were several restrictions of this meta-analysis. First, all the included studies were retrospective studies, indicating an apparent recalling bias and selection bias. Secondly, major
differences were found in pCCA between the West and the East, and the results of subgroup analysis were indeed different. Thirdly, the procedures of radical resection for pCCA were different from different countries [13, 14, 17, 19]. Fourth, the safety of addition resection was not evaluated because postoperative morbidity and mortality was only reported in one study. Fifth, right or left hepatectomy was depended on the Bismuth-Corlette type, which would be affected the prognosis of pCCA, but the data was unavailable. Sixth, margin status including either R-inv or R-cis was the key, but relevant subgroup analysis was unable to conduct due to insufficient data. The last but not the least, publication bias was hard to be avoided, although significant publication bias was not observed in the study.

**Conclusion**

With the current data, we concluded that additional resection should be recommended in selected patients with intraoperative R1, especially in highly experienced centers. However, the standard procedure of radical resection for pCCA and a higher sensitivity and specificity margin examining are badly needed in clinical. In addition, further studies concerning on the types of R1 are also needed.

**Supporting information**

S1 Table. Checklist_PRISMA.
(DOC)

S2 Table. Search strategy in PubMed.
(DOCX)

**Author Contributions**

**Conceptualization:** Lei Wang, Jingfeng Liu.

**Data curation:** Qiao Ke, Yuqing Chen, Qizhen Huang, Nanping Lin.

**Formal analysis:** Qiao Ke, Qizhen Huang, Nanping Lin, Lei Wang.

**Funding acquisition:** Lei Wang, Jingfeng Liu.

**Investigation:** Qiao Ke, Yuqing Chen, Qizhen Huang, Nanping Lin.

**Methodology:** Qiao Ke, Yuqing Chen, Nanping Lin.

**Project administration:** Lei Wang, Jingfeng Liu.

**Resources:** Lei Wang.

**Software:** Qiao Ke.

**Validation:** Qiao Ke, Lei Wang.

**Visualization:** Qiao Ke, Lei Wang.

**Writing – original draft:** Lei Wang.

**Writing – review & editing:** Lei Wang, Jingfeng Liu.

**References**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLO-BOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018, 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID: 30207593
2. Benson AB, D’Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, et al. NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1.2017. Journal of the National Comprehensive Cancer Network. 2017, 15(5):563. https://doi.org/10.6004/jnccn.2017.0059 PMID: 28476736

3. Wakai T, Sakata J, Katada T, Hirose Y, Somai D, Prasoon P, et al. Surgical management of carcinoma in situ at ductal resection margins in patients with extrahepatic cholangiocarcinoma. Ann Gastroenterol Surg. 2018, 2(5):359–366. https://doi.org/10.1002/ags3.12196 PMID: 30238077

4. Mansour JC, Aloia TA, Crane CH, Heimbach JK, Nagino M, Vauthey JN. Hilar cholangiocarcinoma: expert consensus statement. HPB (Oxford). 2015, 17(8):691–699. https://doi.org/10.10111/hpb.12450 PMID: 26172136

5. Esnaola NF, Meyer JE, Karachristos A, Maranik JL, Camp ER, Denlinger CS. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. Cancer Am Soc. 2016, 122(9):1349–1369. https://doi.org/10.1002/cncr.29992 PMID: 26799932

6. Hu HJ, Mao H, Shrestha A, Tan YQ, Ma WJ, Yang Q, et al. Prognostic factors and long-term outcomes of hilar cholangiocarcinoma: A single-institution experience in China. World J Gastroenterol. 2016, 22(8):2601–2610. https://doi.org/10.3748/wjg.v22.i8.2601 PMID: 26937148

7. Gomez D, Patel PB, Lacasias-Purroy C, Byrne C, Sturgess RP, Palmer D, et al. Impact of specialized multi-disciplinary approach and an integrated pathway on outcomes in hilar cholangiocarcinoma. Eur J Surg Oncol. 2014, 40(1):77–84. https://doi.org/10.1016/j.ejso.2013.10.009 PMID: 24262111

8. Stremitzer S, Jones RP, Quinn LM, Fenwick SW, Diaz-Nieto R, Poston GJ, et al. Clinical outcome after resection of early-stage hilar cholangiocarcinoma. Eur J Surg Oncol. 2019, 45(2):213–217. https://doi.org/10.1016/j.ejso.2018.09.008 PMID: 30360988

9. Nagino M, Ebata T, Yokoyama Y, Igame T, Sugawara G, Takahashi Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: A single-center 34-year review of 574 consecutive resections. Ann Surg. 2013, 258(1):129–140. https://doi.org/10.1097/SLA.0b013e3182708b57 PMID: 23059502

10. Zhang XF, Beal EW, Chakeds J, Chen Q, Lu Y, Ethun CG, et al. Defining Early Recurrence of Hilar Cholangiocarcinoma After Curative-intent Surgery: A Multi-institutional Study from the US Extrahepatic Biliary Malignancy Consortium. World J Surg. 2018, 42(9):2919–2929. https://doi.org/10.1007/s00268-018-4530-0 PMID: 29404753

11. Buettner S, Margonis GA, Kim Y, Ganti F, Ethun CG, Poultides G, et al. Conditional probability of long-term survival after resection of hilar cholangiocarcinoma. HPB (Oxford). 2016, 18(6):510–517. https://doi.org/10.1016/j.hpb.2016.04.001 PMID: 27317955

12. Weiss MJ, Cosgrove D, Herman JM, Rastegar N, Kamel I, Pawlik TM. Multimodal treatment strategies for advanced hilar cholangiocarcinoma. Langenbecks Arch Surg. 2014, 399(6):679–692. https://doi.org/10.1007/s00423-014-1219-1 PMID: 24962146

13. Oguro S, Esaki M, Kishi Y, Nara S, Shimada K, Ojima H, et al. Optimal indications for additional resection of the invasive cancer-positive proximal bile duct margin in cases of advanced perihilar cholangiocarcinoma. Ann Surg Oncol. 2015, 22(6):1915–1924. https://doi.org/10.1245/s10434-014-4232-2 PMID: 25404474

14. Ribero D, Amisano M, Lo TR, Rosso S, Ferrero A, Capussotti L. Additional resection of an intraoperative margin-positive proximal bile duct improves survival in patients with hilar cholangiocarcinoma. Ann Surg. 2011, 254(5):776–783. https://doi.org/10.1097/SLA.0b013e3182368f85 PMID: 22042470

15. Zhou Y, Zhang Z, Wu L, Li B. A systematic review of safety and efficacy of hepatopancreatoduodenectomy for biliary and gallbladder cancers. HPB (Oxford). 2016, 18(1):1–6. https://doi.org/10.1016/j.hpb.2015.07.008 PMID: 26776848

16. Fukami Y, Kanoeku Y, Maeda A, Takayama Y, Onoe S. Major hepatopancreatoduodenectomy with simultaneous resection of the hepatic artery for advanced biliary cancer. Langenbecks Arch Surg. 2016, 460(4):471–478. https://doi.org/10.1007/s00423-016-1413-4 PMID: 27023217

17. Ma WJ, Wu ZR, Shrestha A, Yang Q, Hu HJ, Wang JK, et al. Effectiveness of additional resection of the invasive cancer-positive proximal bile duct margin in cases of hilar cholangiocarcinoma. Hepatobiliary Surg Nutr. 2018, 7(4):251–269. https://doi.org/10.21037/hbsn.2018.03.14 PMID: 30221153

18. Otsuka S, Ebata T, Yokoyama Y, Mizuno T, Tsukahara T, Shimoyama Y, et al. Clinical value of additional resection of a margin-positive distal bile duct in perihilar cholangiocarcinoma. Br J Surg. 2019, 106(6):774–782. https://doi.org/10.1002/bjs.11125 PMID: 30899275

19. Zhang XF, Squires MR, Bagante F, Ethun CG, Salem A, Weber SM, et al: The Impact of Intraoperative Re-Resection of a Positive Bile Duct Margin on Clinical Outcomes for Hilar Cholangiocarcinoma. Ann Surg Oncol. 2018, 25(5):1120–1125. https://doi.org/10.1245/s10434-018-6382-0 PMID: 29470820

20. Cillo U, Fondevilla C, Donadon M, Gringeri E, Mocchegiani F, Schiltt HJ, et al: Surgery For Cholangiocarcinoma. Liver Int. 2019, 39 Suppl 1:143–155. https://doi.org/10.1111/liv.14089 PMID: 30843343
21. Mantel HT, Westerkamp AC, Sieders E, Peeters PM, de Jong KP, Boer MT, et al. Intraoperative frozen section analysis of the proximal bile ducts in hilar cholangiocarcinoma is of limited value. Cancer Med. 2016, 5(7):1373–1380. https://doi.org/10.1002/cam4.693 PMID: 27062713

22. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007, 8:16. https://doi.org/10.1186/1745-6215-8-16 PMID: 17555882

23. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 2004, 23(11):2815–2834. https://doi.org/10.1002/stm.649 PMID: 15066327

24. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 2004, 23(11):2815–2834. https://doi.org/10.1002/stm.649 PMID: 15066327

25. Deeks JJ, Altman DG. Analysing Data and Undertaking Meta-Analyses. Cochrane Handbook for Systematic Reviews of Interventions. 2011. Chapter 9:6–14. https://doi.org/10.1002/9780470712184.ch9

26. Wang L, Ke Q, Lin NP, Huang OZ, Zeng YY, Liu JF. The efficacy of transarterial chemoembolization combined with microwave ablation for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Int J Hyperthermia. 2019; 36(1):1288–1296. https://doi.org/10.1080/02656736.2019.1692148 PMID: 31852267

27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003, 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

28. Tsukahara T, Ebata T, Shimoyama Y, Yokoyama Y, Igami T, Sugawara G, et al. Residual Carcinoma In Situ at the Ductal Stump has a Negative Survival Effect: An Analysis of Early-stage Cholangiocarcinomas. Ann Surg. 2017, 266(1):126–132. https://doi.org/10.1097/SLA.0000000000001944 PMID: 27501166

29. Park Y, Hwang DW, Kim JH, Hong SM, Jun SY, Lee JH, et al. Prognostic comparison of the longitudinal margin status in distal bile duct cancer: R0 on first bile duct resection versus R0 after additional resection. J Hepatobiliary Pancreat Sci. 2019, 26(5):169–178. https://doi.org/10.1002/jhbp.619 PMID: 30849218

30. Oter V, Ozer I, Dalgic T, Binarbasi C, Ulas M, Bostanci EB. Results of positive proximal margin after resection for hilar cholangiocarcinoma: An analysis of 42 cases. Turk J Gastroenterol. 2019, 30(1):88–94. https://doi.org/10.5152/tjg.2018.17752 PMID: 30301710

31. Liu F, Ma WJ, Hu HJ, Regmi P, Wang JK, Li FY. The puzzle and challenge in the treatment of an intraoperative margin-positive proximal bile duct in hilar cholangiocarcinoma. Hepatobiliary Surg Nutr. 2017, 6(6):411–413. https://doi.org/10.21037/hbsn.2017.11.05 PMID: 29312978

32. Bagante F, Pawlik TM. ASO Author Reflections: Re-resection of Positive Bile Duct Margin for Hilar Cholangiocarcinoma. Ann Surg Oncol. 2018, 25(Suppl 3):784–785. https://doi.org/10.1245/s10434-018-6865-0 PMID: 30288652

33. Lee JH, Hwang DW, Lee SY, Park KM, Lee YJ. The proximal margin of resected hilar cholangiocarcinoma: the effect of microscopic positive margin on long-term survival. Am Surg. 2012, 78(4):471–477 PMID: 22472407

34. Endo I, House MG, Klimstra DS, Gonen M, D’Angelica M, Dematteo RP, et al. Clinical significance of intraoperative bile duct margin assessment for hilar cholangiocarcinoma. Ann Surg Oncol. 2008, 15(8):2104–2112. https://doi.org/10.1245/s10434-008-0003-2 PMID: 18543039

35. Shingu Y, Ebata T, Nishio H, Igami T, Shimoyama Y, Nagino M. Clinical value of additional resection of a margin-positive proximal bile duct in hilar cholangiocarcinoma. Surgery. 2010, 147(1):49–56. https://doi.org/10.1016/j.surg.2009.06.030 PMID: 19767048

36. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al: Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut. 2012, 61(12):1657–1669. https://doi.org/10.1136/gut-jnl-2011-301748 PMID: 22895392

37. Benavides M, Anton A, Gallego J, Gomez MA, Jimenez-Gordo A, La Casta A, et al. Biliary tract cancers: SEOM clinical guidelines. Clin Transl Oncol. 2015, 17(12):982–987. https://doi.org/10.1007/s12094-015-1436-2 PMID: 26607930

38. Miyazaki M, Yoshitomi H, Miyakawa S, Uesaka K, Unno M, Endo I, et al. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci. 2015, 22(4):249–273. https://doi.org/10.1002/jhbp.233 PMID: 25787274

39. Olthof PB, Miyasaka M, Koerkamp BG, Wiggers JK, Jarnagin WR, Noij T, et al. A comparison of treatment and outcomes of perihilar cholangiocarcinoma between Eastern and Western centers. HPB (Oxford). 2019, 21(3):345–351. https://doi.org/10.1016/j.hpb.2018.07.014 PMID: 30087051
40. Kirstein MM, Vogel A. Epidemiology and Risk Factors of Cholangiocarcinoma. Visc Med. 2016, 32 (6):395–400. https://doi.org/10.1159/000453013 PMID: 28229073

41. Kawashima H, Itoh A, Ohno E, Itoh Y, Ebata T, Nagino M, et al. Preoperative endoscopic nasobiliary drainage in 164 consecutive patients with suspected perihilar cholangiocarcinoma: a retrospective study of efficacy and risk factors related to complications. Ann Surg. 2013, 257(1):121–127. https://doi.org/10.1097/SLA.0b013e318262b2ef PMID: 22895398

42. Chaudhary RJ, Higuchi R, Nagino M, Unno M, Ohtsuka M, Endo I, et al. Survey of preoperative management protocol for perihilar cholangiocarcinoma at 10 Japanese high-volume centers with a combined experience of 2,778 cases. J Hepatobiliary Pancreat Sci. 2019, 26(11):490–502. https://doi.org/10.1002/jhbp.668 PMID: 31520452

43. Olthof PB, Wiggers JK, Groot KB, Coelen RJ, Allen PJ, Besselink MG, et al: Postoperative Liver Failure Risk Score: Identifying Patients with Resectable Perihilar Cholangiocarcinoma Who Can Benefit from Portal Vein Embolization. J Am Coll Surg. 2017, 225(3):387–394. https://doi.org/10.1016/j.jamcollsurg.2017.06.007 PMID: 28687509

44. Parikh AA, Abdalla EK, Vauthey JN. Operative considerations in resection of hilar cholangiocarcinoma. HPB (Oxford). 2005, 7(4):254–258. https://doi.org/10.1080/13651820500373093 PMID: 18333202

45. Nuzzo G, Giuliani F, Ardito F, Giovannini I, Aldrighetti L, Belli G, et al: Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma: results of an Italian multicenter analysis of 440 patients. Arch Surg. 2012, 147(1):26–34. https://doi.org/10.1001/archsurg.2011.771 PMID: 22250108

46. Wiggers JK, Groot KB, Cieslak KP, Doussot A, van Klaveren D, Allen PJ, et al. Postoperative Mortality after Liver Resection for Perihilar Cholangiocarcinoma: Development of a Risk Score and Importance of Biliary Drainage of the Future Liver Remnant. J Am Coll Surg. 2016, 223(2):321–331. https://doi.org/10.1016/j.jamcollsurg.2016.03.035 PMID: 27063572

47. Ebata T, Watanabe H, Ajiake Y, Oda K, Nimura Y. Pathological appraisal of lines of resection for bile duct carcinoma. Br J Surg. 2002, 89(10):1260–1267. https://doi.org/10.1046/j.1365-2168.2002.02211.x PMID: 12296893

48. Kurahara H, Maemura K, Mataki Y, Sakoda M, Iino S, Kawasaki Y, et al. Relationship between the surgical margin status, prognosis, and recurrence in extrahepatic bile duct cancer patients. Langenbecks Arch Surg. 2017, 402(1):87–93. https://doi.org/10.1007/s00423-016-1491-3 PMID: 27491729

49. Ke Q, Wang B, Lin N, Wang L, Liu J. Does high-grade dysplasia/carcinoma in situ of the biliary duct margin affect the prognosis of extrahepatic cholangiocarcinoma? A meta-analysis. World J Surg Oncol. 2019, 17(1):211. https://doi.org/10.1186/s12957-019-1749-7 PMID: 31818290

50. Ratnaveedu ND, Brown AP, Mallett S, Scholten RJ, Patel A, Founta C, et al. Intraoperative frozen section analysis for the diagnosis of early stage ovarian cancer in suspicious pelvic masses. Cochrane Database Syst Rev. 2016, 3:D10360. https://doi.org/10.1002/14651858.CD010360.pub2 PMID: 26930463

51. Yang CH, Lee LY. Pulmonary sclerosing pneumocytoma remains a diagnostic challenge using frozen sections: a clinicopathological analysis of 59 cases. Histopathology. 2018, 72(3):500–508. https://doi.org/10.1111/his.13391 PMID: 28881050

52. Takehara Y. Preoperative assessment of extrahepatic cholangiocarcinoma with imaging. Abdom Imaging. 2004, 29(5):572–580. https://doi.org/10.1007/s00261-004-0191-s PMID: 15363898