Adjuvant chemotherapy improves oncological outcomes of resectable intrahepatic cholangiocarcinoma

A meta-analysis

Ka Wing Ma, FRCS, MS\(^a\), Tan To Cheung, FRCS, MS\(^{a,*}\), Brian Leung, MBBS\(^a\), Brian Wong Ho She, MBBS, FRCS\(^b\), Kenneth Siu Ho Chok, FRCS, MS\(^a\), Albert Chi Yan Chan, MBBS, FRCS\(^a\), Wing Chiu Dai, MBBS, FRCS\(^a\), Chung Mau Lo, MS\(^{a,b}\)

Abstract

Objective: To define the role of adjuvant chemotherapy in the management of resectable intrahepatic cholangiocarcinoma (ICC) by performing a meta-analysis.

Summary background data: Oncological benefit of adjuvant chemotherapy in resectable ICC remains controversial, high-level evidence in such context is lacking.

Method: A comprehensive search using Pubmed, EMbase, and Web of Science was performed from inception to October 2018. Studies compared the survival of patients receiving adjuvant chemotherapy versus surgery alone were included. Data were analyzed using random effect model. Quality of each study and presence of publication bias were assessed by Newcastle–Ottawa score (NOS) and funnel plot with Egger test respectively.

Results: The present meta-analysis included 15 studies (all were retrospective series) and 5060 patients. Adjuvant chemotherapy was administered either intravenously or intra-arterially in the form of trans-arterial chemo-embolization (TACE). The average NOS for the included studies was 6.5. Pooled analysis of the included studies demonstrated significant advantage in the adjuvant chemotherapy group (HR 0.66, 0.55–0.79, \(P\)<.001, \(I^2\)=20.8%). After 2 studies were removed for heterogeneity, advantage of adjuvant chemotherapy remained (HR 0.72, 0.62–0.84, \(P\)<.001, \(I^2\)=0%). Funnel plot suggested no significant publication bias (Egger test, 2-tailed \(P\)=.203). Subgroup analyses suggested that intravenous route of chemotherapy injection (\(P\)<.001) and use of gemcitabine base regimen (\(P\)=.004) are associated with improved overall survival. Adjuvant chemotherapy did not improve disease-free survival in subgroup analysis (\(P\)=.94).

Conclusion: Adjuvant chemotherapy is associated with improved overall survival and should be considered in patients with ICC following curative resection and in particular to patients with advance disease.

Abbreviations: 5-FU = 5-fluorouracil, 95% CI = 95% confidence interval, HR = hazard ratio, \(I^2\) = 1-square, ICC = intrahepatic cholangiocarcinoma, NOS = Newcastle-Ottawa score, TACE = trans-arterial chemoembolization.

Keywords: adjuvant chemotherapy, intrahepatic cholangiocarcinoma, meta-analysis, oncological outcomes

Key Points

- Survivals of ICC were poor even after surgical resection of the tumor, routine adjuvant chemotherapy remained controversial.
- This meta-analysis focused only on ICC which avoid contamination of results by other biliary tract cancers such as Klaskin and carcinoma of common bile duct.
- Adjuvant chemotherapy was associated with improved overall survivals.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC), it contributes to around 10% of all primary liver cancers.\(^{11}\) Being a member of the cholangiocarcinoma...
family, it is considered a distinct disease entity with different pattern of tumor spread and prognosis when compared to cholangiocarcinoma arising from other parts of the biliary system. Unresectable ICC has a grave prognosis with median survival of only 6 to 9 months.[23–27] Complete resection is the only hope of long-term cure, however, the 3-year overall survival of patients after hepatectomy were around 30%.[5–7] This suboptimal oncological outcome sets the stage for studies focusing on factors that can improve long-term survival of the post-hepatectomy patients. Modification of surgical techniques such as radical lymphadenectomy[8–10] and wide resection margin[11,12] had been investigated in some studies, however, the influence of adjuvant chemotherapy on overall survival of resectable ICC remains poorly understood.[13–15] Due to its rarity, there have been no randomized or prospective study comparing the survival outcomes of adjuvant chemotherapy and surgery alone in this context. Furthermore, many of the published series were small retrospective cohort containing a mixture of patients with ICC, peri-hilar, and extrahepatic bile duct cancers with variable resection margin status (i.e., R0, R1, and R2).[16] A well-conducted meta-analysis is required to better analyze the role of adjuvant chemotherapy in resectable ICC. To the best of our knowledge, this is the first meta-analysis investigating the effect of adjuvant chemotherapy on overall survival in patients with resectable ICC.

2. Method

2.1. Search strategy, selection criteria, and data extraction

Systematic literature review was performed to identify articles that are relevant to the present study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A study was regarded as suitable for inclusion if the survival outcome (overall or disease-free survival) between surgery alone group and adjuvant therapy group patients (curative surgery followed by systemic intraavenous or trans-arterial chemo-embolization (TACE)) were reported. Mesh terms including [intrahepatic], [cholangiocarcinoma], and [adjuvant] were used for literature search and only articles written in English were extracted using PUBMED, EMBASE, and WEB OF SCIENCE from inception to October 2018. Approval from Institutional Review Board (IRB) for performing this meta-analysis was not required in our center as it did not involve patients from our locality. The research protocol of the present study has not been registered.

2.2. Search criteria

Two authors (MKW and LB) performed literature search independently. Study was excluded if there was presence of any one of the following conditions:

1) Outcome data contamination by case-mix analysis of intrahepatic and extrahepatic cholangiocarcinoma, such as hilar cholangiocarcinoma (Klaskin tumor), carcinoma of common bile duct, or carcinoma of gallbladder;
2) Radiotherapy as the only adjuvant treatment;
3) Hepatectomy performed in palliative intent (i.e., gross tumorous involvement of resection margin or R2 resection);
4) Direct comparison between adjuvant chemotherapy and surgery alone group not performed,
5) Case number less than 5 in each treatment arm;
6) Hazard ratio (HR) and 95% confidence interval not available or deducible;
7) Review article, conference abstract, and case report.

In addition, we carefully checked the source and period of data collection so as to exclude duplicated data. All the references of the eligible studies were manually checked to avoid missing of relevant papers in the analysis. When different published articles shared part or all of a single data source, we included only the most up-to-date and relevant article.

2.3. Data extraction

Name of first author, country of origin, sample size, study population characteristics, modality of adjuvant treatment, chemotherapeutic regimen, HR with 95% CI of overall and disease-free survivals, and median follow-up duration was extracted from the included studies. When HR and 95% CI were not provided in the full-text, they were estimated using the provided survival data or estimated from the Kaplan–Meier curves using the methods described by Tierney et al.[17] If survival data were provided from both unmatched and matched population in the same article, data from the matched comparison were used for pooled analysis. Discrepancies between reviewers (MKW and LB) during data extraction were resolved by consensus as instructed by the senior author (CTT) of this study. Effort had been made to contact author of the published articles through email in case clarification or further data required.

2.4. Meta-analysis and assessment of publication bias

Meta-analysis was performed to find out the effect of adjuvant chemotherapy on survival after curative resection of ICC using random effect model. Significant heterogeneity was considered if I-square ($I^2$) value equals to 25% or above. Results of meta-analysis were presented by Forest plot. Degree of publication bias was presented by Funnel plot and assessed by Egger test. Significant publication bias was defined as $P$ value below 0.05 (2-sided). Comprehensive Meta-Analysis (CMA) version 3.0 was used for statistical analyses in this study. The authors received no funding to conduct this study.

2.5. Assessment of individual study quality

Robustness of the included studies was evaluated by Newcastle–Ottawa Scale (NOS).[18] Score of 6 or above was regarded as satisfactory quality, while study with score 3 or below was regarded as low quality. Assessment was done by 2 authors (MKW and LB) independently. Discrepancy in assessment was resolved by consensus as per the senior author (CTT).

3. Results

3.1. Overview of the included studies

Initial search identified 1019 eligible studies. After excluding duplicates, 390 articles were screened using title and abstract content. An additional 376 articles were removed according to the exclusion criteria. Finally, 14 studies involving 5060 patients were filtered from the literature (Fig. 1). There was no randomized controlled trial found during the search. Among the 14 studies, 1 was an international multi-center,[19] 1 was a multi-center retrospective series,[20] 1 was a national study using national cancer database[21] and the rest were from single-center retrospective series. Included studies were originated from 3 different continents and 7 countries (Table 1): 4 studies were from the USA,[21–24] 2 from Thailand,[30,31] 1 from...
Japan,

Germany,

Italy,

Korea,

and 1 international multicenter study respectively. Demographic and tumor characteristics of the patient from each study were shown in Table 1. Attempts were made to contact the correspondence author of all included studies for further information but replies were received from 2 centers only. Concerning the chemotherapeutic agents, 5-Fluorouracil and gemcitabine were the most commonly used in the included studies. The case number, follow-up duration, modes of chemotherapy and survival outcomes of each study were presented in Table 2.

| Study (1st author)     | Country | Yr          | Study type | Study size | Sex, male% | Age | R0 resection margin, % | Node positive, % | T-size, cm | Multifocal tumor, % | VI, % |
|------------------------|---------|-------------|------------|------------|------------|-----|------------------------|------------------|------------|---------------------|-------|
| Roayaie S[21]          | USA     | 1991–1997   | RS         | 16         | NS         | 62  | 68.8                   | NS               | 8          | 31.3                | 50    |
| Bhudhisawasdi V[30]    | Thailand| 1998–2002   | RS         | 171        | 67.8       | 56  | 40.9                   | NS               | 75.4%>4cm | 39.2                | 84.8  |
| Wu ZF[24]              | China   | 2005–2006   | RS         | 114        | 77.2       | 56  | 100                    | 9.6              | 52.6%>5cm | 30.7                | 12.3  |
| Ribero G[19]           | Italy   | 1990–2008   | RM         | 404        | 56         | 65  | 88                     | 26               | 6          | 32.3                | 48.6  |
| Luvira V[29]           | Thailand| 2004–2009   | RS         | 50         | 52         | 57.2| 46                     | 64               | 6          | 14                  | NS    |
| Dhanelakiran R[23]     | USA     | 2000–2009   | RS         | 53         | 54.7       | NS  | 75.5                   | 24.5             | 49.1%>5cm | 26.7                | 54.7  |
| Miura J[20]            | USA     | 1998–2011   | RN         | 1970       | 49.4       | 64  | 76.3                   | 17.4             | 39.6%>5cm | NS                  | NS    |
| Liu R[24]              | China   | 2005–2011   | RS         | 81         | 59         | 59  | NS                     | 61.7             | NS         | NS                  | NS    |
| Li J[23]               | China   | 2008–2011   | RS         | 244        | 78.7       | 54  | 100                    | 12.7             | 5.25       | 21.7                | 12.3  |
| Li T[23]               | China   | 2000–2011   | RS         | 211        | 61.5       | 55  | 100                    | 16.1             | 65.9%>5cm | 18                  | 23.7  |
| Kim DH[23]             | Korea   | 1995–2012   | RS         | 215        | 64.2       | 60.2| 92                     | 27               | 5.1        | 17.7                | 30    |
| Okumura S[31]          | Japan   | 2004–2015   | RS         | 109        | 61.5       | 68  | 83.5                   | 29.4             | 4.2        | 23                  | 63.3  |
| Schweitzer N[21]       | Germany | 2000–2015   | RS         | 50         | NS         | NS  | NS                     | 60               | 56%>7.3cm | NS                  | 32    |
| Doussot A[22]          | USA     | 1993–2013   | RS         | 189        | 29.7       | 65.4| 80.4                   | 11.1             | 6.9        | 28.6                | 36    |
| Reames BN              | international | 1990–2015 | RM         | 1154       | 55         | 60  | 87                     | 17               | 71%>5cm   | 22                  | 31    |

N-positive = nodal metastasis, RM = retrospective, multicenter, RN = retrospective, National database, RS = retrospective, single-center, VI = vascular invasion.
3.2. Effect of adjuvant chemotherapy on overall survival

After extraction of HR and 95% CI from the 14 eligible studies, meta-analysis using random-effect model was performed. Superior overall survival for patients who had received adjuvant chemotherapy was demonstrated (HR 0.66, 0.55–0.79, \( P < 0.001, I^2 = 20.8\% \)) (Fig. 2). Two studies (Liu et al\(^{[29]}\) and Schweitzer et al\(^{[33]}\)) reported very large benefit from adjuvant chemotherapy (HR of 0.227 and 0.340 respectively), this was accounted for the relatively heterogeneity in the initial analysis (\(I^2 = 21\% \)). Analysis was repeated after excluding these 2 studies and the advantage of adjuvant chemotherapy still persisted (HR 0.72, 0.62–0.84, \( P < 0.001, I^2 = 0\% \)) (Fig. 3).

### 3.3. Subgroup analysis

3.3.1. Effect of route of chemotherapy administration on overall survival. The route of chemotherapy administration was described in 10 studies. Subgroup analysis was performed for studies in which chemotherapy was given via intravenous route.

#### Table 2

| Study (1st author) | Median FU (month) | Surgery alone, gp, n | Adjuvant chemo, gp, n | Route of adm | Chemo type | DFS (Sur vs adj) HR 95% CI | OS (Sur vs adj) HR 95% CI | NOS |
|-------------------|-------------------|----------------------|----------------------|--------------|------------|--------------------------|--------------------------|-----|
| Roayaie S\(^{[21]}\) | NS 35.7 8 8 | IV 5-FU | 50.5:19.1 | 0.65 | 0.14–3.04 | 41.3:42.9 | 0.792 | 0.123–1.003 | 4 |
| Bhudhisawasdi V\(^{[24]}\) | NS 117 54 | IV 5-FU,MC | NS | NS | NS | NS | 0.56 | 0.39–0.80 | 7 |
| Wu Z\(^{[25]}\) | NS 37 57 | IA 5-FU,CP,HP,ICT | NS | NS | NS | NS | 0.494 | 0.322–0.757 | 9 |
| Ribo\(^{[26]}\) | NS 36.5 318 | 116 NS | NS | 5-FU based | 5.7 | 0.61 | 0.32–1.18 | 7.18 | 0.61 | 0.32–1.18 | 4 |
| Sharma\(^{[27]}\) | NS 32 21 | NS | NS | 75 NS | NS | NS | 23.8:27.6 | 1.238 | 0.50–0.63 | 4 |
| Miru JT\(^{[28]}\) | NS 985 985 | NS | NS | NS | NS | NS | 24.8:23.1 | 0.88 | 0.74–1.06 | 6 |
| Liu R\(^{[29]}\) | NS 63 18 | IV 5,5-FU,CP,DOX,OX | NS | NS | NS | NS | 8.22 | 0.227 | 0.117–0.44 | 4 |
| Liu J\(^{[30]}\) | NS 25.3 122 | 122 IA | 5-FU,CP,HP,ICT | 15.7–22.0 | 0.97 | 0.66–1.42 | 23.2:27.6 | 1.07 | 0.66–1.73 | 6 |
| Li\(^{[31]}\) | NS 17 143 | 68 IA | 5-FU,CP,HP,ICT | NS | 1.69 | 1.09–2.15 | NS | 0.56 | 0.37–0.87 | 8 |
| Kim\(^{[32]}\) | NS 183 | 32 NS | 5-FU,CP,OX,DOX | NS | NS | NS | NS | 0.73 | 0.37–1.43 | 4 |
| Okumura\(^{[33]}\) | NS 62 47 | IV GEM/S-1/both | NS | 0.98 | 0.56–1.37 | NS | 0.66 | 0.38–1.11 | 7 |
| Schweitzer\(^{[34]}\) | NS 25 25 | IV GEM/CS | NS | NS | NS | NS | 18:33.5 | 0.34 | 0.16–0.690 | 8 |
| Doussot A\(^{[35]}\) | NS 42.5 138 | 51 beth GEM (IV) (AI) | 15.26:4 | 0.95 | 0.58–1.56 | NS | NS | NS | NS | 7 |
| Reames BN | NS 807 347 | IV GEM, platinum, 5-FU | NS | NS | NS | NS | 17:10 | 0.6 | 0.49–0.74 | 7 |

95% CI = 95% confidence interval, CP = cisplatin, DFS = disease-free survival, DOX = doxorubicin, EPI = epirubicin, GEM = gemcitabine, HCT = hydroxycamptothecin, HR = hazard ratio, IA = intra-arterial, 5-FU = 5-Fluorouracil, IV = intravenous, NOS = Newcastle-Ottawa Score, NS = not stated, OS = overall survival, CI = cisplatin.

Figure 2. Forest plot illustrating the effect of adjuvant chemotherapy on overall survival.
Pooled analysis of the 5 studies suggested that intravenous chemotherapy was associated with improved overall survival (HR 0.621, 0.491–0.799, I² = 0%, P < .001) (Fig. 4.). No significant survival benefit was demonstrated by the pooled analysis of the 4 studies using intra-arterial (TACE) adjuvant chemotherapy (HR 0.679, 0.313–1.469, I² = 15%, P = .325) (Fig. 5).

3.3.2. Effect of using different chemotherapeutic agents on overall survival. The type of chemotherapeutic agent used for adjuvant treatment was described in 11 studies. There was no significant benefit associated with the use of 5-Fluorouracil (5-FU) based chemotherapy when compared with surgery alone (HR 0.782, 0.560–1.092, I² = 12%, P = .149) (Fig. 6). However, significant survival benefit was shown in the pooled analysis of the 5 studies that incorporated gemcitabine in their chemotherapeutic regimen (HR 0.493, 0.339–0.715, I² = 17.7% P < .001) (Fig. 7).

3.3.3. Effect of adjuvant chemotherapy on disease-free survival. There were 6 studies reported the effect of adjuvant

---

**Table 1**

| Study name          | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|--------------------|--------------|-------------|-------------|---------|---------|
| Roayaie S1         | 0.782        | 0.610       | 1.003       | -1.936  | 0.053   |
| Bhudhisawadi V     | 0.560        | 0.386       | 0.812       | -3.058  | 0.002   |
| Wu ZF              | 0.494        | 0.322       | 0.757       | -3.236  | 0.001   |
| Ribeiro D          | 0.990        | 0.718       | 1.366       | -0.061  | 0.951   |
| Luvira V           | 0.610        | 0.318       | 1.171       | -1.485  | 0.138   |
| Dhanasekaran R     | 1.240        | 0.500       | 3.078       | 0.464   | 0.643   |
| Muira JT           | 0.880        | 0.735       | 1.053       | -1.394  | 0.163   |
| Li J               | 1.068        | 0.660       | 1.729       | 0.268   | 0.789   |
| Li T               | 0.560        | 0.365       | 0.859       | -2.658  | 0.008   |
| Kim DH             | 0.730        | 0.371       | 1.435       | -0.913  | 0.362   |
| Okumura S          | 0.660        | 0.386       | 1.128       | -1.519  | 0.129   |
| Reames BN          | 0.600        | 0.488       | 0.737       | -4.857  | 0.000   |
| Random-effect      | 0.724        | 0.622       | 0.842       | -4.176  | 0.000   |

Heterogeneity: I²: 0%
Z value: -4.176(P<0.001)

---

**Table 2**

| Study name          | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|--------------------|--------------|-------------|-------------|---------|---------|
| Roayaie S1         | 0.782        | 0.610       | 1.003       | -1.936  | 0.053   |
| Bhudhisawadi V     | 0.560        | 0.386       | 0.812       | -3.058  | 0.002   |
| Luvira V           | 0.610        | 0.318       | 1.171       | -1.485  | 0.138   |
| Okumura S          | 0.660        | 0.386       | 1.128       | -1.519  | 0.129   |
| Schweitzer N        | 0.340        | 0.167       | 0.692       | -2.973  | 0.003   |
| Random-effect      | 0.627        | 0.491       | 0.799       | -3.767  | 0.000   |

Heterogeneity: I²: 0%
Z value: -3.767(P<0.001)
chemotherapy on disease-free survival. Most of the study did no show signiﬁcant effect except 1 (Li et al[28]). Pooled analysis showed that adjuvant chemotherapy was not associated with benefit in disease-free survival (HR 0.99, 1.09–2.63, I²=0%, P=.944) (Fig. 8).

3.4. Assessment of publication bias
Publication bias was assessed by funnel plot and there was even distribution of the 14 studies on both side of the mean effect size (Fig. 9). Egger test suggested that there was no signiﬁcant publication bias in the current meta-analysis (P=.203, 2-tailed, t value 1.36)

3.5. Assessment of the quality of the included studies
The overall quality of the included studies was satisfactory with mean NOS of 6.5. Majority of the studies achieved a good quality grading, ranging from NOS 6 to 8, mainly due to clear record of the patient’s characteristic, exposure, and event documentation. None of the included studies received a poor NOS score, and 6 studies were graded as average (i.e., NOS of 4 out of 9) due to possible selection bias, signiﬁcant confounders between the comparing groups and unclear documentation or insufﬁcient follow-up duration (Table 3).

4. Discussion
The current meta-analysis concluded that use of adjuvant chemotherapy is associated improved overall survival when compared with surgery alone for patients with resectable ICC. Subgroup analyses suggested that intravenous chemotherapy administration and gemcitabine base adjuvant chemotherapy were associated with improved overall survival. However, TACE and 5-FU base adjuvant chemotherapy were not associated with survival beneﬁt. No signiﬁcant improvement was demonstrated in the use of adjuvant chemotherapy regarding disease-free survival. This study represents the ﬁrst study to elucidate the effect of adjuvant chemotherapy in patients with resectable ICC using meta-analysis.

| Study name | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|--------------|-------------|-------------|---------|---------|
| Wu ZF      | 0.494        | 0.322       | 0.757       | -3.236  | 0.001   |
| Liu R      | 0.227        | 0.117       | 0.440       | -4.388  | 0.000   |
| Li J       | 1.068        | 0.660       | 1.729       | 0.268   | 0.789   |
| Li T       | 1.610        | 1.033       | 2.508       | 2.105   | 0.035   |
| Random-effect | 0.679    | 0.313       | 1.469       | -0.984  | 0.325   |

Heterogeneity: I²: 15.1%
Z value: -0.984(P=0.325)

Figure 5. Subgroup analysis on the effect of intra-arterial adjuvant chemotherapy versus surgery alone group.

| Study name | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|--------------|-------------|-------------|---------|---------|
| Roayaie S  | 0.782        | 0.610       | 1.003       | -1.936  | 0.053   |
| Bhudhisawadhi V | 0.560     | 0.386       | 0.812       | -3.058  | 0.002   |
| Wu ZF      | 0.494        | 0.322       | 0.757       | -3.236  | 0.001   |
| Luwra V    | 0.610        | 0.318       | 1.171       | -1.485  | 0.138   |
| Li J       | 1.068        | 0.660       | 1.729       | 0.268   | 0.789   |
| Li T       | 1.610        | 1.033       | 2.508       | 2.105   | 0.035   |
| Random-effect | 0.782    | 0.560       | 1.092       | -1.443  | 0.149   |

Heterogeneity: I²: 11.6%
Z value: -1.443(P=0.149)

Figure 6. Subgroup analysis on the effect of using 5-FU based adjuvant chemotherapy versus surgery alone group.
Survival benefit of adjuvant chemotherapy as illustrated in the meta-analysis of 14 studies was significantly contributed by the study from Schweitzer et al. and Liu et al. Their disproportionately low HRs were related to a more advance disease stage in these 2 study populations as reflected by the high percentage of nodal involvement (i.e., over 60%). For the sake of reducing heterogeneity, these 2 studies were excluded and the benefit of adjuvant chemotherapy still remained, though to a lesser extent, suggesting that the beneficial effect of adjuvant chemotherapy might be more pronounced in node-positive ICC patients. Yet, this statement requires further studies to confirm.

Due to the intrinsic inflammatory mediating property of cholangioocyte, cholangiocarcinoma is inherently a chemoresistant cancer.\cite{35,36} With the development of chemotherapeutic agents, there was a significant improvement in the response rate of up to 30% to 50% after switching the first-line chemotherapeutic agent from 5-FU to gemcitabine.\cite{37–39} Because of the lower response rate of ICC to 5-FU base chemotherapy, a much larger sample size is required to demonstrate the survival benefit of adjuvant chemotherapy using 5-FU, and that explains the negative finding of the subgroup analysis of 5-FU base chemotherapy in this study.

### Table 1: Hazard Ratio and 95% CI for Survival Benefit of Adjuvant Chemotherapy in ICC

| Study name    | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---------------|--------------|-------------|-------------|---------|---------|
| Liu R         | 0.227        | 0.117       | 0.440       | -4.388  | 0.000   |
| Kim DH        | 0.730        | 0.371       | 1.435       | -0.913  | 0.362   |
| Okumura S     | 0.660        | 0.386       | 1.128       | -1.519  | 0.129   |
| Schweitzer N  | 0.340        | 0.167       | 0.692       | -2.973  | 0.003   |
| Reames BN     | 0.600        | 0.488       | 0.737       | -4.857  | 0.000   |
| Random-effect | 0.493        | 0.339       | 0.715       | -3.727  | 0.000   |

**Meta Analysis**

Figure 7. Subgroup analysis on the effect of using gemcitabine based adjuvant chemotherapy versus surgery alone group.

### Table 2: Hazard Ratio and 95% CI for Survival Benefit of Adjuvant Chemotherapy in ICC

| Study name    | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |  
|---------------|--------------|-------------|-------------|---------|---------|
| Roayaie S     | 0.650        | 0.139       | 3.029       | -0.549  | 0.583   |
| Luvira V      | 0.610        | 0.318       | 1.171       | -1.485  | 0.138   |
| Li J          | 0.970        | 0.661       | 1.423       | -0.156  | 0.876   |
| Li T          | 1.690        | 1.088       | 2.625       | 2.335   | 0.020   |
| Okumura S     | 0.880        | 0.563       | 1.376       | -0.560  | 0.575   |
| Doussot A     | 0.950        | 0.579       | 1.558       | -0.203  | 0.839   |
| Random-effect | 0.990        | 0.749       | 1.308       | -0.071  | 0.944   |

**Meta Analysis**

Figure 8. Forest plot illustrating the effect of adjuvant chemotherapy on disease free survival.
landmark paper from Valle et al (ABC-02 trial) suggested that combination of gemcitabine with platinum group cytotoxic agents provides better oncological control than gemcitabine alone in locally advanced or metastatic biliary tract cancer. The role of this gemcitabine-platinum base chemotherapeutic regimen in the context of adjuvant treatment has yet to be defined. We demonstrated a protective effect in patients using gemcitabine base chemotherapy over surgery alone group (Fig. 7); however, heterogeneity could be substantial among the studies used in this subgroup analysis, that is, gemcitabine alone or in combination with platinum or non-platinum cytotoxic agents, route of drug administration, dosage, and duration are some of the potential confounders. A randomized controlled trial with well-designed patient enrolment and treatment protocol is eagerly awaited to further clarify this issue.

Concerning the efficacy of different routes of chemotherapy administration, there has been no direct comparison between systemic intravenous and TACE in the literature. From our subgroup analyses, clear survival benefit of using systemic intravenous adjuvant chemotherapy was demonstrated (HR 0.627, 0.491–0.799, \( P < .001 \)). On the contrary, no significant benefit in overall survival could be shown in the TACE subgroup (HR 0.679, 0.313–1.469, \( P = .325 \)). The authors were more in favour of systemic intravenous as the route of adjuvant chemotherapy administration, since majority of the ICC recurrences are extra-hepatic; Regional nodal basins, peritoneum, lung, and bones are common sites of treatment failure, and systemic adjuvant treatment should be a better option to eradicate small metastatic foci in these areas. In addition, TACE induces tissue hypoxia by blocking hepatic artery, this promotes neo-vascularization and possibly facilitates the spread of any residual ICC cells; these issue is particularly of concern in patients who had close resection margin. Nonetheless, TACE is associated with good side-effect profile and is well-tolerated by over 80% of the patients, it could still be an option for patients with marginal physiological reserve and poor tolerance to systemic chemotherapy before further evidence emerged.

Studies investigating the effect of adjuvant chemotherapy on disease-free survival were scarce. This is probably related to the fact that ICC patients usually have a limited disease-free survival even after curative hepatectomy making it difficult to demonstrate any treatment effect with small case number. Among the 6 studies (Fig. 8) that presented the effect of adjuvant chemotherapy on disease-free survival, 5 of them showed no significant benefit. Study from Li et al was the only 1 which demonstrated a “bi-polar” effect in the use of adjuvant TACE for ICC patients (i.e., adjuvant TACE was associated with benefit in overall survival but at the same time leading to an inferior disease-free survival). According to the explanation from Li et al, this was partly related to patient selection (i.e., TACE tends to benefit more in patients with advanced disease), and partly related to the 2 effects associated

Table 3

| Study            | Selection | Comparability | Outcome | Total |
|------------------|-----------|---------------|---------|-------|
| Roayaie S        | **        | **            | **      | 4     |
| Bhudhisawarsi V  | **        | **            | **      | 7     |
| Wu ZF            | **        | **            | **      | 8     |
| Ribero D         | **        | **            | **      | 7     |
| Luvira V         | **        | **            | **      | 4     |
| Dhanasekaran R   | **        | **            | **      | 4     |
| Miura J          | **        | **            | **      | 6     |
| Liu R            | **        | **            | **      | 4     |
| Li J             | **        | **            | **      | 6     |
| Li T            | **        | **            | **      | 7     |
| Kim DH           | **        | **            | **      | 4     |
| Okumura S        | **        | **            | **      | 7     |
| Schweitzer N     | **        | **            | **      | 7     |
| Dousset A        | **        | **            | **      | 7     |
| Reames BN        | **        | **            | **      | 8     |

NOS = Newcastle–Ottawa Score.
with TACE; Embolization of the hepatic artery leads to growth factor release from ischemic tissue favours local recurrence while chemotherapeutic agents dissipated in the hepatic parenchyma helps to suppress the growth of any recurrent tumor.

There were some limitations in the current analysis; first, majority of the studies included were single center retrospective series, some studies did not present data about margin and nodal status and this might weaken the power of the meta-analysis. Inclusion of qualitative assessment (i.e., the NOS system) for each study helps readers to understand the nature of the studies. Second. Toxicity from adjuvant chemotherapy was not analyzed, as this information were not available in most of the included series, a separate study focusing on the severity and incidence of toxic effect would help to address this problem. In addition, the proportion of ICC patient who received concurrent or sequential external radiation was not clearly documented in most of the included study, and its effect could not be evaluated in this current analysis. The message derived from this meta-analysis should prompt future randomized controlled trial which is able to propose a generalizable treatment protocol and better quantify the anticipated oncological benefit in different patient strata.

5. Conclusion

The results from this meta-analysis suggested that adjuvant chemotherapy are associated with improved overall survival and should be offered to ICC patients following curative hepatectomy, in particular, those who had more advanced disease. Systemic intravenous route of chemotherapy administration with the use gemcitabine base regimen are the preferred approach.

Acknowledgment

The authors would like to thank Mr Henry Tam (MSc (Epi&Kbiostat)) and Mr HK Yuen (BSc (Hons)(stat&comp)) for the statistical support.

The author would like to thank Dr Vor Luivira (Khon Kaen University, Thailand), Dr Kenya Yamanaka and Professor Etsuro Hatano (Kyoto University Hospital, Japan) for their kind reply and generous sharing of study data.

Author contributions

Conceptualization: Ka Wing Ma, Tan To Cheung, Brian Wong. Hoi She, Kenneth Siu Ho Chok, Albert Chi Yan Chan, Jeff Wing Chiu Dai, Chung Mau Lo.

Data curation: Ka Wing Ma, Brian Leung.

Formal analysis: Ka Wing Ma, Brian Leung.

Investigation: Ka Wing Ma, Tan To Cheung.

Methodology: Ka Wing Ma, Tan To Cheung.

Project administration: Tan To Cheung.

Supervision: Tan To Cheung, Chung Mau Lo.

Visualization: Tan To Cheung, Brian Wong Hoi She, Kenneth Siu Ho Chok, Albert Chi Yan Chan, Jeff Wing Chiu Dai, Brian Leung, Chung Mau Lo.

Writing – original draft: Ka Wing Ma.

Writing – review & editing: Ka Wing Ma, Ka Wing Ma orcid: 0000-0002-6072-4874.

References

[1] Aljiffry M, Abdulelah A, Walsh M, et al. Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. J Am Coll Surg 2009;208:134–47.

[2] Weimann A, Varnholt H, Schilt H, et al. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma. Br J Surg 2000;87:1182–7.

[3] Chu K-M, Lai EC, Al-Hadeed S, et al. Intrahepatic cholangiocarcinoma. World J Surg 1997;21:301–6.

[4] Berdah S, Delpejo P, Garcia S, et al. A western surgical experience of peripheral cholangiocarcinoma. Br J Surg 1996;83:1517–21.

[5] de Jong MC, Nathan H, Sotopoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 2011;29:3140–5.

[6] Paik KY, Jung JC, Hoe JS, et al. What prognostic factors are important for resected intrahepatic cholangiocarcinoma. J Gastroenterol Hepatol 2007;22:766–70.

[7] Farges O, Fuku D. Clinical presentation and management of intrahepatic cholangiocarcinoma. Gastroenterol Clin Biol 2010;34:191–9.

[8] Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84–96.

[9] de Jong MC, Nathan H, Sotopoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol Off J Am Soc Clin Oncol 2011;29:3140–5.

[10] Farges O, Fuku D, Le Treut YP, et al. AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma: by the AFC-BHCC-2009 study group. Cancer 2011;117:2170–7.

[11] Farges O, Fuku D, Boledowski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-BHCC-2009 study group. Ann Surg 2011;254:824–9.

[12] Ma KW, Cheung TT, She WH, et al. The effect of wide resection margin in patients with intrahepatic cholangiocarcinoma: a single-center experience. Medicine 2016;95:e4133.

[13] Zhu AX, Knox JJ. Adjuvant therapy for intrahepatic cholangiocarcinoma: the debate continues. Oncologist 2012;17:1504–7.

[14] Shen WF, Zhong W, Liu Q, et al. Adjuvant transcatheter arterial chemoembolization for intrahepatic cholangiocarcinoma after curative surgery: retrospective control study. World J Surg 2011;35:2083–91.

[15] Morise Z, Sugio A, Tokoro T, et al. Surgery and chemotherapy for intrahepatic cholangiocarcinoma. World J Hepatol 2010;2:58–64.

[16] Thongprasert S. The role of chemotherapy in cholangiocarcinoma. Ann Oncol 2005;16(suppl 2):ii93–6.

[17] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

[18] Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.

[19] Reames BN, Bagante F, Ezej A, et al. Impact of adjuvant chemotherapy on survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. HPB Off J Int Hepato Pancreato Biliary Assoc 2017;19:901–9.

[20] Ribeiro D, Pinna AD, Guglielmi A, et al. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. Arch Surg (Chicago, Ill. 1960) 2012;147:1107–13.

[21] Miura YT, Johnston FM, Tsi S, et al. Chemotherapy for surgically resected intrahepatic cholangiocarcinoma. Ann Surg Oncol 2015;22:3716–23.

[22] Rosayrie S, Guarrera JV, Ye MQ, et al. Aggressive surgical treatment of intrahepatic cholangiocarcinoma: predictors of outcomes. J Am Coll Surg 1998;187:365–72.

[23] Dossou AB, Grooth-Koerkamp B, Wiggers JK, et al. Outcomes after resection of intrahepatic cholangiocarcinoma: external validation and comparison of prognostic models. J Am Coll Surg 2015;221:452–61.

[24] Dhanasekaran R, Hemming AW, Zendejas I, et al. Treatment outcomes and prognostic factors of intrahepatic cholangiocarcinoma. Oncol Rep 2013;29:1259–67.

[25] Lu Z, Liu S, Yi Y, et al. Serum gamma-glutamyl transferase levels affect the prognosis of patients with intrahepatic cholangiocarcinoma who receive postoperative adjuvant transcatheter arterial chemoembolization: a propensity score matching study. Int J Surg (Lond, Engl) 2017;37:24–8.

[26] Wu ZF, Zhang HB, Yang N, et al. Postoperative adjuvant transcatheter arterial chemoembolisation improves survival of intrahepatic cholangiocarcinoma patients with poor prognostic factors: results of a large
monocentric series. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 2012;38:602–10.

[27] Li J, Wang Q, Lei Z, et al. Adjuvant transarterial chemoembolization following liver resection for intrahepatic cholangiocarcinoma based on survival risk stratification. Oncologist 2015;20:640–7.

[28] Li T, Qin LX, Zhou J, et al. Staging, prognostic factors and adjuvant therapy of intrahepatic cholangiocarcinoma after curative resection. Liver Int Off J Int Assoc Study Liver 2014;34:953–60.

[29] Liu RQ, Shen SJ, Hu XF, et al. Prognosis of the intrahepatic cholangiocarcinoma after resection: hepatitis B virus infection and adjuvant chemotherapy are favorable prognosis factors. Cancer Cell Int 2013;13:99.

[30] Luivira V, Euroboonyanun C, Bhudhisawasdi V, et al. Patterns of recurrence after resection of mass-forming type intrahepatic cholangiocarcinomas. Asian Pacific J Cancer Prev APJCP 2016;17:4735–9.

[31] Bhudhisawadi V, Talabmin C, Pugkhem A, et al. Evaluation of postoperative adjuvant chemotherapy for intrahepatic cholangiocarcinoma patients undergoing R1 and R2 resections. Asian Pacific J Cancer Prev APJCP 2012;suppl 13:169–74.

[32] Okumura S, Kaido T, Hamaguchi Y, et al. Impact of skeletal muscle mass, muscle quality, and visceral adiposity on outcomes following resection of intrahepatic cholangiocarcinoma. Ann Surg Oncol 2017;24:1037–45.

[33] Schweitzer N, Weber T, Kirstein MM, et al. The effect of adjuvant chemotherapy in patients with intrahepatic cholangiocarcinoma: a matched pair analysis. J Cancer Res Clin Oncol 2017;143:1347–55.

[34] Kim DH, Choi DW, Choi SH, et al. Is there a role for systematic hepatic pedicle lymphadenectomy in intrahepatic cholangiocarcinoma? A review of 17 years of experience in a tertiary institution. Surgery (United States) 2015;157:666–75.

[35] Weihe H, Henson R, Meng F, et al. Interleukin-6 contributes to growth in cholangiocarcinoma cells by aberrant promoter methylation and gene expression. Cancer Res 2006;66:10517–24.

[36] Fava G, Alpini G, Rychlicki C, et al. Leptin enhances cholangiocarcinoma cell growth. Cancer Res 2008;68:6752–61.

[37] Verderame F, Russo A, Di Leo R, et al. Gemcitabine and oxaliplatin combination chemotherapy in advanced biliary tract cancers. Ann Oncol 2006;17(suppl 7):vii68–72.

[38] Hezel AF, Zhu AX. Systemic therapy for biliary tract cancers. Oncol 2008;13:415–23.

[39] Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;96:896–902.

[40] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. New Engl J Med 2010;362:1273–81.

[41] Shim JH, Park JW, Kim JH, et al. Association between increment of serum VEGF level and prognosis after transcutaneous arterial chemoembolization in hepatocellular carcinoma patients. Cancer Sci 2008;99:2037–44.

[42] Sergio A, Cristofori C, Cardin R, et al. Transcutaneous arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 2008;103:914–21.

[43] Liu L, Ren ZG, Shen Y, et al. Influence of hepatic artery occlusion on tumor growth and metastatic potential in a human orthotopic hepatoma nude mouse model: relevance of epithelial–mesenchymal transition. Cancer Sci 2010;101:120–8.

[44] Gupta S, Kobayashi S, Phongkitkarun S, et al. Effect of transcatheter hepatic arterial embolization on angiogenesis in an animal model. Invest Radiol 2006;41:516–21.

[45] Burger I, Hong K, Schuhk R, et al. Transcutaneous arterial chemoembolization in unresectable cholangiocarcinoma: initial experience in a single institution. J Vasc Int Radiol Jvir 2005;16:553–61.

[46] Gusani NJ, Balaa FK, Steel JL, et al. Treatment of unresectable cholangiocarcinoma with gemcitabine-based transcatheter arterial chemoembolization (TACE): a single-institution experience. J Gastrointest Surg Off J Soc Surg Aliment Tract 2008;12:129–37.