CCO CHINESE CLINICAL ONCOLOGY
AN OPEN ACCESS JOURNAL FOR CLINICAL CANCER RESEARCH WITH CURRENT AND PRACTICAL INFORMATION

Peer Review File

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Reviewer A

Comment 1: The authors summarize current situations for diagnosis, surgical resection, and systemic treatment for cholangiocarcinoma.

The authors should describe current situations and future prospective for treatments in patients with advanced and unresectable cholangiocarcinoma, because most targeted therapies have been developed for patients with advanced disease. In this manuscript, they have never introduced standard therapies for them. The authors should introduce more in detail regarding current situations and clinical trials for targeted therapies including immunotherapies with checkpoint inhibitors. Details in diagnosis and surgical resection are not necessary for this manuscript.
Reply 1: We have included current treatment for advanced ICC as described in ABC-02. As we describe targeted therapies throughout the paper, we have indicated the clinical settings in which these therapies are used that (i.e., advanced disease, metastatic disease).

We appreciate this comment. We respectfully believe that diagnosis and surgical resection are critical portions to the management of iCCA , which is not a common disease and resection offers the only chance of "cure". Furthermore, there has been ongoing debate over lymph node dissection and margin status, which are important to address in a comprehensive review of management and treatment.
Changes in text: page 12-13, lines 265-274:
Palliative Treatment
Unfortunately, most patients presenting with iCCA have advanced disease that is resectable. Based on the phase III ABC-02 trial data, cisplatin plus gemcitabine versus gemcitabine alone was established as the standard of care for advanced biliary tract cancers.[40] This trial randomized 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive cisplatin plus gemcitabine versus gemcitabine alone. After a median follow-up of 8.2 months, median overall survival was superior in the cisplatin-gemcitabine group at 11.7 months versus 8.1 months in the gemcitabine group ($p<0.001$). ABC-02 established cisplatin plus gemcitabine as the standard of care therapy for patients with advanced biliary tract tumors, including individuals with iCCA.

Comment 2: Gemcitabine plus cisplatin has never shown a survival benefit as adjuvant therapy in phase III studies. This combination chemotherapy is a standard first-line therapy for advanced disease. I do not agree with the descriptions in this manuscript (page 4 lines 79-81, and page 12 lines 247-248).
Reply 2: We appreciate this comment and have revised the text to indicate that capecitabine showed a survival benefit in the adjuvant setting.
Changes in the text: page 4, lines 86-89: In regards to systemic chemotherapy, the multi-center phase III BILCAP trial examined the efficacy of adjuvant chemotherapy in which a survival benefit was shown in a per-protocol analysis for capecitabine over

observation (OS 53 months versus 36 months, p=0.028).[7]

Comment 3: The authors should update the descriptions in this manuscript. I heard that infigratinib and futibatinib have been approved by the FDA. Most of phase III trials for FGFR2 inhibitors in first-line therapy have been discontinued due to poor accrual.
Reply 3: It is true that infigratinib and futibatinib have FDA approval for advanced or metastatic ICC; however, phase III trials are still undergoing to determine efficacy versus gemcitabine/cisplatin (accrual still in process as of June 2, 2022). We have edited the text to reflect that these drugs have FDA approval but are still being investigated on clinical trials to determine efficacy over current standard of care.
Changes in the text:
Page 13, lines 282-284: Many of these targeted therapies have received FDA approval for use in the advanced or metastatic CCA setting; however, the efficacy of these agents over standard of care treatment is still being investigated.
page 14, lines 313-315: With recent FDA approval for advanced or metastatic CCA, infigratinib is currently under investigation in a phase III trial against gemcitabine/cisplatin as first line therapy for advanced or metastatic CCA.[49]

Reviewer B

In this review article the authors offer a narrative review of the diagnosis, surgical resection, and systemic treatment of intrahepatic cholangiocarcinoma. Although it is an important topic there are some issues that would need to be fixed.

Major issues
Comment 4. Similar related reviews about intrahepatic cholangiocarcinoma have been published, such as, PMID: 36400328, PMID: 32606456, PMID: 35053523, PMID: 35961708, PMID: 34904492, and so on. The authors should identify what EXISTING REVIEWS have shared and what gap existing reviews existed in the Introduction. Based on the gap, the authors MUST clearly analyze and clarify the new information this narrative review provide.
Reply 4: This was an INVITED review with this REQUESTED TOPIC. We agree that reviews presenting should seek to provide new information rather than only summarizing what is already known. This has been addressed in the text as below with some of the above PMIDs have been included in the references.
Changes in the text: page 5, lines 93-105: Due to the dismal overall survival for iCCA at all stages, there exists a significant need for novel molecular diagnostics and targeted therapies. Previous reviews have summarized the latest trends in molecular alterations and the development of targeted therapy in iCCA.10-12 These reviews are important in the context of highlighting new treatment regimens. Given the poor outcomes following standard treatment of iCCA, targeted therapy and systemic chemotherapy have been a topic of much interest in addition to surgical resection for resectable disease. The current clinical review addresses surgical resection and novel agents as potential management options to improve patient survival. In particular, many patients often do not present with resectable disease; therefore, novel agents are need to facilitate downstaging disease to make surgery possible. In addition, novel targeted agents may provide for more effective adjuvant therapy following surgery, as well as destination therapy for patients with unresectable disease. The current review addresses the

diagnosis, staging, surgical management, late-breaking clinical trials and the current use of targeted therapies in the management of iCCA.

Comment 5. The authors said the objective of this review is to summarize current guidelines for diagnosis, surgical resection, and systemic treatment, however, I failed to found the related guidelines' recommendation for clinical reference in the manuscript. For example, in the BILCAP trial, the authors could specify "Based on the partial benefits reported in the BILCAP trial, international guidelines published in 2019 recommend adjuvant capecitabine for a period of 6 months following curative resection of CCA as the current standard of care (PMID: 30856044)". The authors should consider adding the content.

Reply 5: We appreciate this point. While clinical guidelines have been changed to include capecitabine in the adjuvant setting, data are still emerging relative to changes regarding targeted therapies. We did revise the paper to emphasize the point that guidelines have been changed to include adjuvant capecitabine. In regard to diagnosis and surgical resection, we referenced NCCN guidelines and other international studies earlier in the manuscript.

Changes in the text: page 11, lines 226-229: Consequently, international clinical practice guidelines were updated in 2019 to recommend adjuvant capecitabine for 6 months as the current standard of care following iCCA resection for most patients, especially those with high-risk features.

Comment 6: "Recommendations for intrahepatic cholangiocarcinoma management" should be considered to provide in the Table for the readers' convenience. The authors could summarized the recommendations from the current guidelines. The authors also should pay attention to the clinical situation which was not well solved according to the current guidelines and provide a reasonable recommendation and outlook based on the latest research data, which would be the important clinical value of the review for the clinician.

Reply 6: We appreciate this comment. We have added a paragraph at the end of review under conclusions which summarizes our recommendations for patients who are not resectable or may be borderline resectable.

Changes in the text: pages 17-18, lines 382-392:

Recommendations for intrahepatic cholangiocarcinoma management

Patients with resectable iCCA should undergo surgical resection and receive adjuvant gemcitabine, which has been suggested to improve disease free and overall survival. Patients with unresectable disease or borderline resectable disease should be treated with cisplatin plus gemcitabine. The goal of systemic chemotherapy is to prolong survival, potentially convert unresectable disease to resectable disease, as well as test the biology of borderline resectable tumors to determine who may benefit from surgery. Among patients who do not respond to first line chemotherapy, targeted therapies should be strongly considered based on the molecular profile of the iCCA. Given the high incidence of recurrence and possible need for targeted therapy, all patients with iCCA should have molecular analysis of the tumor to identify potential targeted therapy that may benefit them in addition to standard of care chemotherapy.

Comment 7: The current Tables 2-5 missing some important clinical trials investigating targeted therapies for iCCa. The clinical trials about intrahepatic cholangiocarcinoma is not only 17 when searched in the ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=Intrahepatic+Cholangiocarcinoma&Search

=Apply&recrs=e&age_v=&gndr=&type=Intr&rslt= ; https://clinicaltrials.gov/ct2/results?cond=Intrahepatic+Cholangiocarcinoma&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=). The authors should confirm this vital information. The authors are also encouraged to merge the Tables 2-5 together as one Table.

Reply 7: We appreciate this point. We have clarified the text to reflect that these tables are a representative summary of ongoing targeted therapy trials and is not exhaustive. The included trials are whose which focused on patients with specific tumor mutations.

Changes in the text: page 16, lines 358-359: Important to note, the included trials focused on patients with specific tumor mutations; of note, trials that included patients without mutations were not included.

Comment 8: The authors stated in the Introduction "This review focuses on late-breaking clinical trials and the current use of targeted therapies in the management of iCCA". However, the authors only summarized the related clinical trials in the tables. The major concern of the current manuscript locates in the lack of in-depth analysis for those key clinical trials. The authors should logically specify the core information in the tables in at least 2-3 paragraphs.

Reply 8: We have expanded the summary of the paper in the conclusions section.

Changes in the text: pages 17-18, lines 382-392:

Recommendations for intrahepatic cholangiocarcinoma management

Patients with resectable iCCA should undergo surgical resection and receive adjuvant gemcitabine, which has been suggested to improve disease free and overall survival. Patients with unresectable disease or borderline resectable disease should be treated with cisplatin plus gemcitabine. The goal of systemic chemotherapy is to prolong survival, potentially convert unresectable disease to resectable disease, as well as test the biology of borderline resectable tumors to determine who may benefit from surgery. Among patients who do not respond to first line chemotherapy, targeted therapies should be strongly considered based on the molecular profile of the iCCA. Given the high incidence of recurrence and possible need for targeted therapy, all patients with iCCA should have molecular analysis of the tumor to identify potential targeted therapy that may benefit them in addition to standard of care chemotherapy.

Minor issues

1. Title

Please consider using a more informative title. The current content in the manuscript is not only focused on the targeted therapies but refers to many aspects of intrahepatic cholangiocarcinoma. In the title, also clearly identify this manuscript as a narrative review.

Reply 9: We have adjusted the title accordingly.

Changes in text: page 1, lines 2-3: Narrative Review: Current Management and Novel Targeted Therapies in Intrahepatic Cholangiocarcinoma

2. Abstract

(1) The abstract does not convey the purpose of the paper. In particular, the abstract does not indicate the information about the current clinical trials in management of intrahepatic cholangiocarcinoma.

Reply 10: We have edited the background and objective section of the abstract to further emphasize the importance of clinical trials.

Changes in text: page 2, lines 28-32: The development of improved targeted therapies

is critical to prolonged overall survival, and the use of targeted agents for ICC is currently the focus of several ongoing randomized controlled trials. The objective of this review is to summarize current guidelines for diagnosis, surgical resection, and systemic treatment, which includes ongoing clinical trials investigated targeted therapies.

(2) A subsection "Conclusions" should be provided in the Abstract. The authors should describe the main conclusions and how the review may potentially impact future researches, clinical practice and policy making in this part.
Reply 11: We have included a conclusions section as below.
Changes in text: pages 2-3, lines 43-48: Conclusions: Surgical resection represents the mainstay of treatment followed by 6 months of adjuvant capecitabine. While additional data is needed through randomized controlled trials, targeted therapies including FGFR, IDH, and ErbB2 inhibitors offer promising results as adjuncts to current standard of care in iCCA, particularly among individuals with unresectable disease. Future recommendations regarding the use of targeted therapy will emerge as clinical trial data become available.

3. Introduction
I would suggest to the authors add detailed information about "the survival benefit of the gemcitabine plus cisplatin", especially the superiority both in terms of progression-free survival and overall survival.
Reply 12: We have further expanded on the results of the BILCAP trial as below.
Changes in text: page 4, lines 86-89: In regards to systemic chemotherapy, the multi-center phase III BILCAP trial examined the efficacy of adjuvant chemotherapy in which a survival benefit was shown in a per-protocol analysis for capecitabine over observation (OS 53 months versus 36 months, p=0.028).

4. Clinical presentation and evaluation
Para 4: The updated 8th edition of the AJCC staging manual should be cited.
Reply 13: We have added AJCC 8th edition citation. Changes were first made in AJCC 7th edition which is why the 7th edition was mentioned specifically in the text. Clarification was made to why 7th edition was mentioned.
Changes in text: page 7, line 159: classification was set forth in the revised initially in the 7th edition of the AJCC staging system

5. A separate paragraph on strengths and limitations of the review should be provided in the main body to promote a more intellectual interpretation.
Reply 14: We have included a strength/limitations in the review conclusions section.
Changes in text: page 17, lines 372-380 This review had several strengths and limitations. The current review provided a comprehensive summary of the diagnosis, surgical management, and use of systemic and targeted therapies – including an up-to-date review of ongoing clinical trials. These data are valuable to clinicians who treat patients with iCCA. Targeted therapy and personalized medicine have resulted in recent changes in treatment guidelines and offers patients with advanced disease additional options for treatment. While this review provided a summary of the latest evidence, the field of precision medicine continues to move quickly. As such, information included in the review was not exhaustive and not all currently recruiting clinical trials involving patients without targetable mutations were included.

6. Abbreviations

Abbreviations need to be defined when used for the first time in the full-text. Please check: ABSTRACT section: Intrahepatic cholangiocarcinoma (iCCA). Clinical presentation and evaluation: what is EGD.

Reply 15: Abbreviations have been fixed. EGD defined as below

Changes in text: page 7, line 154: Esophagogastroduodenoscopy (EGD) and colonoscopy are

7. Tables

Please revise this statement in Table 1: Date of Search (specified to date, month and year) should be “October 1, 2022”; Timeframe should be “January 1, 1997-October 1, 2022”.

Reply 16: Changes have been made as seen below

Changes in text: page 24, lines 605-606: (clinicaltrials.gov, accessed on 20 October 2022, dates of search January 1, 1997-October 1, 2022).