

SPECIFIC COMMENTS TO AUTHORS

The authors reviewed the morphological subtypes, epidemiology, etiology, mutation patterns, clinical manifestation, and diagnosis methods in the INTRODUCTION. Then, the authors reviewed various methods of liquid biopsy and illustrated the characteristic value in detection, treatment, monitoring and prognosis of CCA. This review covers almost all the current liquid biopsy methods, with clear logic and focused points. There are two minor revision that are essential. 1. At the line 5 paragraph5 of INTRODUCTION, the authors referred the features and advantages of CT and MRI. The opinion and the reference might be wrong. According to clinical commons and a lot of clinical studies, the MRI has absolutely advantage in discriminating between iCCA and HCC, evaluating the relationship of the tumor with the adjacent structures, the extent of local invasion. Please refer to more additional and updated research and make appropriate modification. 2. At the line 17 paragraph5 of INTRODUCTION, the authors mentioned that “fine-needle aspiration (FNA) that comes at the price of a high risk of tumor seeding”. This is a rather obsolete point of view. For recent decade, FNA have shown not significantly increase the risk of cancer spread. Actually, the most important risk of liver FNA is bleeding and infection. Please add more appropriate reference.

- **Many thanks for the pertinent comments, we edited the paragraph and relative references on the roles of CT and MRI in the “INTRODUCTION” section according to the reviewer’s recommendation.**
- **We edited the paragraph and relative references on the role of FNA in CCA modifying the statement about possible risks and complications and updating with more appropriate references as suggested by the reviewer.**

Reviewer's code: 02992461

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Liquid biopsy (LB) has been involved in a very active research field and gained remarkable attention. CCA still represents an unsolved challenge for clinicians and researchers. Therefore, this manuscript aimed to address the role of LB in CCA and proposed that LB would be as minimally invasive screening and diagnostic biomarkers, prognostic tools and therapeutic monitoring targets. (1) Additional information would be necessary to identify the difference or inner relationship between cfDNA and ctDNA (2) There are still some grammatical errors, such as "is is present..."

- **Many thanks for the pertinent comments, we expanded the "CIRCULATING TUMOUR DNA (ctDNA)" paragraph with additional information and references on cfDNA and ctDNA as suggested.**
- **We had the final version of the manuscript fully revised by a native English speaker Author (AGW)**

- **We edited the manuscript according to the editorial recommendations: the references cited in the text are in square brackets, the reference list includes DOI and PMID numbers and all authors are now listed.**