Dear editor and reviewer,

Thank you very much for your corrections and suggestions to improve this manuscript. We have added new bibliography and we wish to know if, in case of definitive publication, you can order it.

We attach our revisions in the following lines:

REVISOR 1. ID: 00722050

The authors describe the diagnostic and therapeutic aspects of cholangiocarcinoma and the review is good apart of some misspelling (e.g., hepatocarcinoma) and the following remarks. I am missing plentiful of imaging for such manuscripts. I expect 6-10 images of cholangiocarcinoma. I didn't see the PRISMA criteria or a flowchart. We need to have a systematic review using the PRISMA criteria if we want to publish in 2019. The title needs to be amended mirroring the only aspects that the manuscript is covering.

We can add the images that you request in the format that you wish. Please, indicate the format and we will attach them.

We add at the end of paper the PRISMA flowchart.

We propose the next title: "Diagnostic-therapeutic management of bile duct cancer".

REVISOR 2. ID: 00052926

Page 6 The authors stated "Bile duct–type iCCA has an almost exclusively mass-forming growth pattern, is often associated with chronic liver disease (viral hepatitis or cirrhosis), and is not preceded by preneoplastic lesions. In clinical-pathological terms, it is similar to hepatocarcinoma and is positive for cytokeratin (CK). Furthermore, bile duct–type iCCA (mucinous) generally appears as a mass-forming pattern, periductal infiltration, or intraductal growth. It is more frequently associated with PSC and may be preceded by preneoplastic lesions. It shares phenotypical traits with pCCA and pancreatic cancer." Which one of the iCCA mentioned in this paragraph is the conventional type and which one the bile ductular type?

We indicate the type at the text as follows:

"Furthermore, conventional bile duct–type iCCA (mucinous) generally appears as a mass-forming pattern, periductal infiltration, or intraductal growth. It is more…"

Page 7 The authors stated "Endoscopic ultrasound (EUS)–guided fine needle aspiration (FNA) has been shown to have a good diagnostic yield: Please specify diagnostic accuracy (sensitivity, specificity, PPV, NPV).

Thank you for the suggestion, we add it.

Page 8 The authors stated "It is important to point out that, given duodenal access, all of the endoscopy techniques we describe below are more accurate and efficacious in the diagnosis of dCCA. "Please identify the diagnostic accuracy.

Thank you for the suggestion, we add them.

Page 8 The authors stated "In addition, histopathology-based diagnosis (histology or cytology) represents a challenge in many cases owing to the high rate of false negatives". Please specify the numbers.

We add the rate of false negatives.

Page 9. The authors stated "However, unfortunately, the sensitivity of tissue diagnosis based on ERCP, especially cytology, is low (from 18% to 48%, increasing modestly to 59.4% when techniques (Please report the techniques) are combined), although the specificity is very high (please specify the rates of specificity)

The techniques are biopsy and cytology guided by ERCP, with a specificity approximated of 100%. We add it.

Page 10. The authors stated "It has proven to be more accurate than CT and PET for assessment of regional lymph node metastasis in patients with mainly distal Ecca (please define what is Ecca)"

Ecca is actually eCCA and it is referred to an extrahepatic cholangiocarcinoma. We add the definition at the beginning of the article.

Page 10. The citation number "79" was changed because it was recently published. "Primrose JN, et al BILCAP study group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol. 2019 Mar 25. pii: S1470-2045(18)30915-X." Please replace.

Thank you for the update. We have replaced the citation and modified the text as follows:

"The benefit of adjuvant chemotherapy was explored in the phase III BILCAP trial, in which 447 patients with resected BTC (368 with intrahepatic, hilar, or extrahepatic CCA) were randomly assigned to receive 8 cycles of capecitabine compared with placebo. The intent to treat analysis revealed a potentially clinically relevant but not statistically significant improvement in OS (median 51 vs 36 months; HR, 0.81; 95% CI, 0.63-1.06). However, the benefit was statistically significant when a per protocol analysis was performed (median 53 vs 36 months; HR, 0.75; 95% CI, 0.58-0.97)[79].

Results from another recently published phase III trial comparing adjuvant treatment with gemcitabine monotherapy versus placebo…"

Page 11. The addition of nanoparticle albumin-bound (nab)-paclitaxel to gemcitabine-cisplatin for the treatment of patients with advanced biliary tract cancer seems promising. (Shroff RT, et al. Gemcitabine, Cisplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers: A Phase 2 Clinical Trial. JAMA Oncol. 2019 Apr 18.) Please mention it in the section "SYSTEMIC TREATMENT FOR ADVANCED DISEASE"

Thank you very much for the suggestion. We have added this information in the section "Systemic treatment for advanced disease"

"Based on recent studies, the addition of nanoparticle albumin-bound (nab)-paclitaxel to gemcitabine-cisplatin for the treatment of patients with advanced biliary tract cancer seems promising[90]."

Page 12. Cholangiocarcinoma is considered as a chemoresistant tumour. Chemosensitization strategy to improve the response of CCA is recently under discussion (Lozano E, et al. Causes of hOCT1-dependent cholangiocarcinoma resistance to sorafenib and sensitization by tumor-selective gene therapy. Hepatology. 2019) and should be mentioned in the "Molecular Targeted Therapy" section.

Thank you for the appreciation. We have included this information in the "Molecular Targeted Therapy" section.

"Cholangiocarcinoma is considered as a chemoresistant tumour. Chemosensitization strategy to improve the response of CCA is recently under discussion[102]."