Reviewer's report

Title: Mutational profiling reveals PIK3CA mutations in gallbladder carcinoma

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Reviewer: Francesco Leone

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The paper from Deshpande et al. aims at identifying novel or targetable mutations in biliary carcinoma. Owing to the lack of effective therapies for unresectable biliary carcinoma, the purpose is sustainable and the methods employed are clearly explained.

However, several weak points have to be evidenced:

Major Compulsory Revisions:

-The authors stated that there are important differences among tumors having different anatomic origin in the biliary tree, but they have chosen to group intra-hepatic and perihilar carcinoma. Since the characteristics and the prognosis of these two entities are different (J Surg Oncol. 2010 101:111-5), they should explain this choice.

-Not only resected tumors have been included in the analysis. In fact in “Methods” it is described that samples were indentified from “resected or biopsied” archived tissues. If this is true, I cannot understand how (Table 3) all of the 33 gallbladder carcinoma have a complete TNM staging. Seven patients have a stage IV disease, and they have been classified as T1-4 and N0-2. In these cases a Tx or Nx is rather expected.

-Distal extra-hepatic (n=6) and intrapancreatic biliary carcinoma (n=9) (in Table 1 referred as to middle CBD and intrapancreatic chlangiocarcinoma) have been distinguished by peri-hilar carcinoma (n=5). One out of five peri-hilar tumor has KRAS mutation, but no KRAS mutation have been found in 13 extra-hepatic carcinoma. Then, the author conclude that it is possible that KRAS mutation previously described in extra-hepatic biliary tumors may be misdiagnosed peri-biliary pancreatic carcinoma. I believe that the statement is not supported by the evidence. A statistical analysis should be included to define whether KRAS mutation may be confined to intra-hepatic/perihilar carcinoma (4/27).

-Since this work is descriptive and does not contain novelty which can immediately affect the menagment of patients with biliary cancer, preclinical models should be set up to argument the statement “this data points towards deregulation of PI3K signaling as a key event in the molecular pathogenesis of BTC (“Discussion”).

Minor Essential Revisions:

The abbreviation CBD is not explained in the text. Does it mean common bile
duct?
The abbreviation IBD is not explained in the text. Does it mean internal review board?
In Table 3 the four PIK3CA mutations are all E545K whereas in Table 2, two of them are E542K.

Discretionary Revisions
A systematic review of previously identified genetic alteration of key regulatory genes involved in biliary carcinoma cell proliferation and invasiveness might improve the global impact of this work.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests