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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 14679
Title: Prognostic analysis of the distribution of neutrophils in cholangiocarcinoma
Reviewer's code: 02861223
Reviewer's country: Denmark
Science editor: Jing Yu
Date sent for review: 2014-10-20 17:49
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[Y] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair	[ ] Grade D: Rejected	BPG Search:	[ ] Rejection
[ ] Grade E: Poor		[ ] Existing	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

The presented work provides evidence for a role of CD15-positive neutrophils in the prognosis of cholangiocarcinoma. The authors investigated the intra-tumoral expression of CD15 by immunohistochemistry in patients who underwent surgery for cholangiocarcinoma (intrahepatic and extrahepatic). It resulted in a postulated correlation between high expression levels of CD15 and a decreased disease free survival and overall survival. Assuming a prognostic role of neutrophils in tumor biopsies, the therapeutic choices could be affected and targeted therapy could be an option. Critique and concerns: ? Please specify the number of analyzed cases (291 vs. 254) in the abstract. Please provide exact numbers of tumor patients in this study. Authors claim that 291 patients have been investigated...however, in table 2 the number of patients is 254? What does off-chip means? ? Please do not use abbreviations in the abstract and explain abbreviations when first used in the manuscript ? Abstract is of poor English quality and for the inexperienced reader in this scientific field not easily to understand. ? Please use a consistent way of citation. ? There is missing information about the pathogenesis of the studied cases of cholangiocarcinoma. It appears important to report on patients with CCC and underlying Crohn's disease or colitis ulcerosa. ? The provided tumor tissue score for CD15 evaluation appears to be based on staining intensity, percentage of positive cells and score calculating formula, however, this is not stated clearly. Please refine and provide profound explanation for how the score and how patient/tumor selection into High and

Low was defined! Further, please provide names and initials of the two independent pathologists who evaluated CD15 expression ? Please re-evaluate with a statistician, if 13 cases are indeed sufficient to make a point about TNM IV-stage and CD 15 expression. ? 74 R1 Patients and 217 R0 resected patients with CCC. How authors evaluated CD15 Expression regarding R classification. How R margin status impacts CD15 significance in CCC? ? Of great importance is the fact that the authors claim CD15 proves to be an independent prognostic factor in CCC, because of significant results in the multivariate analysis. However, the data provided in this manuscripts do not support this concept, as in the COX regression only tumor differentiation ($p<0.004$), margin (R) status ($p<0.014$) and TNM stage ($p<0.001$), but not CD15 expression ($p=0.073$!!), deliver significant p values and, thus present prognostic independence! Why do the authors then claim CD15 to be an independent prognosticator? ? The discussion gives an overview about published data concerning the relationship between prognosis of different tumor entities and inflammatory markers, mainly CD15 positive granulocytes in the tumor-environment. A review about the clinical value of those findings is missing. ? The interpretation of the results is not adequate. It firstly lacks a statement about the incoherence concerning a risk assessment on disease recurrence (multivariate vs. univariate analysis). Secondly, it lacks thoughts about a relation between CD15 positive neutrophils and tumor progression as well as a possible target function. Up-to-date literature about “immune” targeted-therapy in cholangiocarcinoma is missing. ? Please correct the key of figure 2 ? The cited literature is not up to date. Please review the literature