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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 12692
Title: Management of hepatocellular carcinoma: Predictive value of immunohistochemical markers for postoperative survival
Reviewer code: 02929478
Science editor: Ling-Ling Wen
Date sent for review: 2014-07-23 21:42
Date reviewed: 2014-07-28 23:55

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] 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	[ ] Major revision

COMMENTS TO AUTHORS

This is an excellent review of an important topic that would be of interest to many journal readers. There are no major and few minor concerns. Regarding the latter, in the section on HMGB1 DNA binding nuclear proteins, the authors could elaborate on how the process could be dramatically "sped up" when cytoplasmic localization of HMGB1 binds with RAGEs. In addition, the second sentence of the section dealing with CK19 appears to have been misplaced (belonging in the CD133 discussion). Finally, there are a small number of typographical errors.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 12692
Title: Management of hepatocellular carcinoma: Predictive value of immunohistochemical markers for postoperative survival
Reviewer code: 00069297
Science editor: Ling-Ling Wen
Date sent for review: 2014-07-23 21:42
Date reviewed: 2014-07-27 03:33

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair	[ ] Grade D: Rejected	BPG Search:	[ ] Rejection
[ ] Grade E: Poor		[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This review discussed recent progress in research focused mainly on the most promising immunohistochemical prognostic markers in predicting the postoperative survival of HCC patients. This is an interesting study and the discuss is appropriate. The conclusion seems to be fair. The contents would give significant information. The language need to be improved.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 12692
Title: Management of hepatocellular carcinoma: Predictive value of immunohistochemical markers for postoperative survival
Reviewer code: 02860875
Science editor: Ling-Ling Wen
Date sent for review: 2014-07-23 21:42
Date reviewed: 2014-07-30 05:56

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[Y] Grade D: Fair	[ ] Grade D: Rejected	BPG Search:	[ ] Rejection
[ ] Grade E: Poor		[ ] Existing	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

Thank you for asking me to review this manuscript reviewing the evidence for different IHC markers in predicting the outcome after hepatic resection for HCC. The review is extensive and covers a large number of potential markers from a very large number of studies. I have the following comments about the manuscript. Major I would think that the manuscript should be re-structured to make it more accessible. There is a discussion, within the conclusions, about what IHC features are important to become more widely clinically applicable. I think that this should be moved to the front of the article as this is fundamentally the most important aspect. What are the characteristics of the ideal IHC biomarker for HCC? Clearly it needs to be repeatable, with strong localized staining, valid across a number of patient groups and HCC subtypes, easily quantified and associated with clear clinical outcome measures. I would reduce the amount of discussion devoted to targets that are not realistic for implementation and concentrate on targets such as ki67 that are genuinely feasible for widespread clinical implementation. Further, we have to be clear about what we are using these markers for. If they are simply going to predict who is going to recur post-resection, is there any evidence for biomarker driven enhanced surveillance in altering that outcome? Or would they be better to guide resection versus percutaneous ablative therapy or directing the patient straight to consideration for transplantation. Discussing a number of markers that are also mutated in HCC is slightly illogical. IHC will never tell us about the mutation status of these proteins.

Minor 1. The review states in the abstract, core tip and introduction that hepatic resection is the 'most curative' treatment strategy for HCC. This is clearly not true, as liver transplantation has been demonstrated in multiple studies to have better long-term tumour related outcomes. 2. In the introduction the authors state: "and the major reason for the low postoperative survival rate is widespread intrahepatic metastasis or invasion[6]." There are clearly 2 phases of tumour recurrence: early relating to intrahepatic metastases or occult synchronous HCC and late relating to metachronous HCC development. Therefore the above statement is not correct as stated. 3. In the section on TP53 the authors state: "role of p53 in tumor initiation as well as its malignant progression". I would restate to state that p53 is one of the most frequently mutated genes in HCC and that the loss of p53 is associated with a worse prognosis. I am not sure that wild-type p53 plays a role in tumour initiation. 4. You cannot state that on multivariate analysis p53 is not associated with outcome independent of tumoral phenotype and then 6 lines later state: "When combined with clinopathological parameters, there is an adverse impact of p53 expression on survival." The multivariate analysis shows that you can get the same information just from the clinicopathological data. 5. Fundementally, IHC can tell you nothing about the mutation status of TP53. We know from sequencing studies that TP53 most often has missense rather than truncating mutatiions (Please see COSMIC database). IHC antibodies will always have difficulty in detecting proteins with a small number of missense AAs. Therefore the studies with high p53 expression by IHC reflect both high wild-type and mutant p53 which are clearly very different situations. 6. When discussine E-Cadherin, you should discuss the significant literature describing loss of ECDH with the epithelial-mesenchymal transition. 7. You have not mentioned any phospho-specific antibodies as potential biomarkers for HCC. These markers give some indication about pathway activation, rather than simply increased protein expression and therefore the potential for actionable targets. This would include phospho-S6 where several studies have demonstrated

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 12692
Title: Management of hepatocellular carcinoma: Predictive value of immunohistochemical markers for postoperative survival
Reviewer code: 00503849
Science editor: Ling-Ling Wen
Date sent for review: 2014-07-23 21:42
Date reviewed: 2014-07-31 16:11

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
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[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This manuscript extensively reviewed the predictive value of almost all available immunohistochemical markers for postoperative survival in patients with hepatocellular carcinoma. This manuscript can provide useful information to readers. I recommend publishing this manuscript.