

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 50116

Title: Estimating the survival benefit of adjuvant therapy based on bayesian network prediction model in curative resected advanced gallbladder adenocarcinoma

Reviewer's code: 00057659

Reviewer's country: Germany

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-07-05 09:23

Reviewer performed review: 2019-07-05 09:39

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This study supports the recent knowledge of the advantage of adjuvant radiochemotherapy in advanced stages of gall bladder carcinoma in a large amount of patients.



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INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 50116

Title: Estimating the survival benefit of adjuvant therapy based on bayesian network prediction model in curative resected advanced gallbladder adenocarcinoma

Reviewer's code: 03252981

Reviewer's country: Japan

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-07-08 03:18

Reviewer performed review: 2019-07-14 02:26

Review time: 5 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The paper describes the factors associated with prognosis gall bladder cancer, which were identified by Bayesian network using database of Surveillance, Epidemiology, and End Results. The authors found that the survival time was associated with adjuvant



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chemoradiotherapy, radiotherapy and chemotherapy, rather than surgery alone. The model and statistical calculations appears reasonable. If the authors add the informations, the readers can understand the article easily. Figures needs more explanations. For example, it is unclear what "?" means in Figure 2 and what is the difference in black and blue arrows. There are many grammatical mistakes. Also, there are many strange sentences and wordings. The manuscript needs thorough revision.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

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- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 50116

Title: Estimating the survival benefit of adjuvant therapy based on bayesian network prediction model in curative resected advanced gallbladder adenocarcinoma

Reviewer's code: 03492099

Reviewer's country: Germany

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-07-09 06:09

Reviewer performed review: 2019-07-19 13:03

Review time: 10 Days and 6 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

It is an interesting paper and developed a prediction model of survival for curative resected advanced gallbladder adenocarcinoma. However, I still have some suggestion to the author. It is an interesting paper and developed a prediction model of survival

for curative resected advanced gallbladder adenocarcinoma. However, I still have some suggestion to the author. General comments 1. For the suture of this paper, I suggested that the authors performed the cox regression to determine the independent factors of survival, then evaluate the importance of these independent factors, and then using these independent factors to develop the prediction model and evaluate the efficacy of the model. 2. I agree with the authors that using “survival time ≤ 9 ” and “survival time > 9 ” to split patients in table 2 and Figure 2. However, I am curious the results that using “survival” and “death” to split patients. Can the authors performed the assays in comment 1 using “survival” and “death” to split patients? 3. Disease specific survival is also a stable parameter to evaluate the survival of patients, and several publications which obtain patients from SEER database have included this endpoint. Thus, it will be very nice that the author can evaluate the prediction model in disease specific survival, or develop another model for predicting in disease specific survival. Thus, can the authors performed the assays in comment 1 using disease specific survival? 2. Please use “chemotherapy”, “radiotherapy”, and “chemoradiotherapy” instead of “CTx”, “XRT”, and “cXRT” in the abstract and the whole manuscript. 3. Please defined what is “Scope Reg LN Sur”, “Number Ln”, “Surg Oth Reg”, “Surg Prim Site”, “positive Ln” in the abstract and the whole manuscript? 4. Usually the median was followed by interquartile range. Thus, please provide the interquartile range in the whole manuscript. 6. The authors statement that: “In order to evaluate the model performance more accurately, 70% (574) of patients formed the training dataset to establish Bayesian model and the remaining 30% (244) patients were considered as the testing dataset to test the model.” The data were spited randomly? If it is, please describe how they performed the randomization. 7. It would be very nice that the authors can reported their finding according to TRIPOD and cited the paper (Moons K G M, Altman D G, Reitsma J B, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or

Diagnosis (TRIPOD): explanation and elaboration. *Annals of internal medicine*, 2015, 162(1): W1-W73.) 8. I am do not understand which parameter were adopted to develop the prediction model. The parameters presented in Fig. 2 or parameters presented in Table 3. The author MUST defined clearly in the text. In addition, the cox regression is MUST be performed before the development of the model. This will allow that the authors only include independent parameters in this model. 9. The authors state that: "Moreover, although this study was performed using the SEER database, the study population was only 818 patients after screening. Large volume, prospective, randomized controlled clinical trials are therefore needed to validate the prediction model in the future." To solve the limitation of small sample size, I suggested the author performed 10-fold cross-validation or bootstrap (Kohavi R. A study of cross-validation and bootstrap for accuracy estimation and model selection//Ijcai. 1995, 14(2): 1137-1145.) 12. For patient selection, as far as I know that some patients lost the information of lymph node, T-stage, radiation, chemotherapy, etc. (https://seer.cancer.gov/manuals/2018/SPCSM_2018_maindoc.pdf). Did the author also excluded these patients? 13. The author should declare the limitation of the radiation therapy and chemotherapy information of SEER database (<https://seer.cancer.gov/data/ChemotherapyRadiation-SEER-DUA.pdf>) 14. The author should declare who access the SEER data (<https://seer.cancer.gov/data/access.html>) and Treatment Data (<https://seer.cancer.gov/data/treatment.html>)

Other comments

1. Title The main results and conclusions of this manuscript is that the authors developed a robust prediction model for curative resected advanced gallbladder adenocarcinoma. Thus, it would be very nice that the author can put "prediction model" in the title.

2. Abstract "The probability of a survival time of > 9.0 months was associated with, in order of the highest to lowest, adjuvant chemoradiotherapy (cXRT) > XRT > CTx > surgery alone, for patients with node-positive disease, the model predicted

a larger benefit from xCRT" I do not understand what the authors want to tell the reader. Please re-write this sentence. 3. Introduction "The role of adjuvant therapy for GBC, however, is not well-known at this time." Please add one reference here. 4. Method 4.1 "We removed patients who did not have the ICD-0-3 codes 8140, 8141, 8143, or 8147, which designate adenocarcinoma." Please add one reference which use the ICD-0-3 code to collect patients from SEER database. 4.2 "The variable of age was divided into three intervals of 19 to 64 years, 65 to 75 years, and 76 to 97 years. Positive Ln was divided into three intervals of 0, 1 to 3, and > 3. Number Ln was divided into four intervals of 0, 1 to 3, 4 to 6, and > 6. Tumor size was divided into four intervals of 0 to 10 mm, 11 to 30 mm, 31 to 50 mm, and > 50 mm based on medical definitions" To determine the threshold (cut-off), the author should perform ROC curve and Youden Index (Kumar R, Indrayan A. Receiver operating characteristic (ROC) curve for medical researchers. Indian pediatrics, 2011, 48(4): 277-287.) 4.3 "In some datasets, when the number of negative and positive cases varies, the accuracy may not be the appropriate criteria. Considering this condition, the receiver operating characteristic (ROC) curve and the area under the curve (AUC) were calculated to measure the overall performance of the classification model further." Please write clearly in which dataset, such as in Fig.x or in Table x. 4.4 "All continuous variables were transformed to discrete variables for BN analysis and expressed with frequency and percent. Categorical variables were presented with frequency and percent. Survival curve was estimated with the Kaplan-Meier method and the results were compared with the log-rank test. " See comments 4.2. To determine the threshold (cut-off) of continuous variables, the author should perform ROC curve and Youden Index (Kumar R, Indrayan A. Receiver operating characteristic (ROC) curve for medical researchers. Indian pediatrics, 2011, 48(4): 277-287.) 5. Results 5.1 The authors state that: "Out of the patients who received radiation, only 4 (0.49%) received it before surgery, while 222 (27.14%) received it after surgery. Regarding

chemotherapy, 345 (42.18%) underwent it, while 473 (57.82%) did not.” For patients receiving radiation, 0.49% received it before surgery and 27.14% received it after surgery, however, what the other 72.37% of patients received? For patients not receiving chemotherapy (473), my feeling is that some of these patients were indicated “Unclear” or “Not available” (<https://seer.cancer.gov/data/treatment.html>). If this is true, please defined these patients in the text, figures, and the tables. Please do the same with patients receiving radiation. 5.2. “When the follow-up was cut-off in December 2015” How the authors obtained this information? 5.3 “The results of confusion matrix are listed in Table 2. There were 114 patients whose survival time was less than 9 months and 130 patients who had a survival time of longer than 9 months. “ In table 2 the authors only presented results of testing data set. I would be very nice that the authors can show the results of training dataset in the same table. 5.4 “A total of 83 patients were correctly classified as having survival time ≤ 9 months and 86 patients were classified as having survival time of > 9 months, based the probability threshold of 0.5.” I agree with the authors that using “survival time ≤ 9 ” and “survival time > 9 ” to split patients in table 2 and Figure 2. However, I am curious the results that using “survival” and “death” to split patients. Can the authors show me the results as they did in table 2 and Figure 2. In addition, how the authors defined the threshold of 0.5? Please write clearly. 5.5 “Prognostic factors ranked by importance” I think the cox regression followed by the importance measure should be presented before the authors introduce the model. This means I suggested that the authors performed the cox regression to determine the independent factors of survival, then evaluate the importance of these independent factors, and then using these independent factors to develop the prediction model and evaluate the efficacy of the model. 5.6 “The results indicated that the radiation was the most important prognosis factor influencing survival time after radical resection for advanced GBC patients.” I still think the cox regression is necessary to

support this conclusions. This means only adjusted other risk factors, the radiation is still an independent risk factor. Then the authors can concluded that radiation is a prognosis factor of patients. Only based on this point (radiation is a prognosis factor of patients), evaluating the importance is valuable, and this is same to other parameters. 5.7 “We combined the BN model and importance measures to select radiation, chemotherapy, T-stage and N-stage as the observation variables.” I do not understand that why combined the BN model and importance measures, the authors can select radiation, chemotherapy, T-stage and N-stage as the observation variables. Please write clearly. 5.8 “For patients with node-negative disease, the model estimated the similar survival benefit from the addition of XRT and cXRT, regardless of T3 or T4 stage. For example, for a patient with T3N0 disease, his/her probability of a survival time of > 9 months with surgery alone, CTx, XRT, cXRT was 41.35%, 58.29%, 75.42% and 76.62%, respectively. For patients with node-positive disease, the model predicted a small survival benefit from CTx and XRT, and a larger benefit from xCRT. For example, for a patient with T4N1 disease, his/her probability of a survival time of > 9 months with surgery alone, CTx, XRT, cXRT was 14.85%, 37.03%, 43.14% and 57.97%, respectively.” Please take out “similar”, “large” from the text, because these subjective words do not give objective information to the readers. Please write down the true number, such as “his/her probability of a survival time of > 9 months with surgery alone, CTx, XRT, cXRT was 41.35%, 58.29%, 75.42% and 76.62%, respectively” 5.9 “The median OS for the advanced GBC patients..... (Figure 3)” In Figure 3, the authors performed this analysis using the entire patients, thus advanced GBC patients, is not correct, because some of the patients are early stage of GBC. 5.10 “There was a significant difference among the different adjuvant therapy groups (log rank, P=0.000) (Figure 3).” Firstly, P=0.000 is not correct, because P-value never be zero. Please correct as $P < 0.001$. Secondly, what is the meaning of the P-value, for comparing Surgery alone vs. CTx? Or for comparing



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Surgery alone vs. XRT. Please write the P-value of each comparing in the figure legends. Thirdly, the information of patients receiving chemoradiotherapy is missing in Table 1. Please add these information. 5.11 In the discussion section, please avoid using words such as “advanced” to describe GBC. In addition, avoid using “small” and “large” to describe survival benefit.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

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- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No