Peer Review File

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Reviewer A:

General Comments

Authors retrospectively evaluated the treatment effect of Camrelizumab plus Apatinib as an adjuvant therapy for HCC with microvascular invasion. As authors mentioned, vascular invasion is an established risk of HCC recurrence. Recent ICI combination therapy might be promising for such patients. Therefore, this study was interesting, but several issues remained to be addressed.

Reply: We appreciate the kind comments and positive feedback of the reviewer. We cherish the opportunity for the manuscript to be revised.

Specific Comments

Comment 1: Viral etiology should be clarified. The risk of HCC occurrence is different between HBV and HCV. The presence of hepatitis virus control should also be mentioned.

Reply 1: Thank you very much for your kind suggestion. We think your consideration is right. We therefore refined the data on HBV and HCV of the enrolled patients, and performed cox regression analyses for RFS and OS. For patients with chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV) infection or both, patients with no obviously abnormal liver function can receive hepatectomy as soon as possible, and appropriate antiviral therapy is routinely and consistently administered after hepatectomy. Thank you again for your kind consideration.

Changes in the text: We added baseline data for HBV and HCV in **Table1**, and presented the results of cox regression analyses in **Table2**. In the "Interventions, follow-up, and outcomes" section of the manuscript, we briefly described antiviral therapy for patients with chronic hepatitis. (**see Page 5, line 30**)

Comment 2: The pattern of recurrence (e.g. local recurrence, distant intrahepatic

recurrence or extrahepatic recurrence) should be clarified. Early recurrence was frequent in present study.

Reply 2: Thank you for your valuable comments. We revisited the follow-up medical records of 155 patients with recurrence (32 (32.3%) in the adjuvant therapy group and 123 (71.5%) in the observation group), and counted patterns of recurrence. According to your comments, we compared the patterns of recurrence between the two groups tabularly, and the results indicated that the patterns of recurrence were similar between both groups. Thanks again for your comments.

Changes in the text: We added Table S1 to show the results of recurrence patterns (**see Supplementary Material 1, Table S1**). And we have modified the description in the "Efficacy Analysis" section of the manuscript (**see Page 9, line 9**).

Comment 3: The treatment after recurrence should be also described.

Reply 3: Thank you for your valuable comments. We revisited the follow-up medical records of 155 patients with recurrence (32 (32.3%) in the adjuvant therapy group and 123 (71.5%) in the observation group). According to your comments, we presented the treatment after recurrence in both groups tabularly. Thanks again for your comments.

Changes in the text: We added Table S2 to show the treatment after recurrence in both groups (**see Supplementary Material 1, Table S2**).

Comment 4: Regarding with AE, hepatitis might be irAE. Authors should show the detail of AEs, especially those requiring steroid.

Reply 4: Thank you very much for your valuable comments. According to your comments, we reviewed the follow-up medical records of all 111 patients enrolled in the adjuvant therapy group, counting TRAEs of any grades as detailed as possible. We agree with you very much about hepatitis being irAEs. Therefore, we paid special attention to the use of steroid in TRAEs of all grades. We hope that our manuscript will meet your requirements and obtain your approval. Thanks again for your comments.

Changes in the text: We have modified our Table 3 to show the TRAEs of the adjuvant therapy group in as much detail as possible (**see Table, Table 3**). And we added the

description of steroid use in the "Safety Analysis" section of the manuscript (**see Page 11, line 6**).

Reviewer B:

General Comments

I read with interest the multicentre propensity score matched study comparing observation alone versus adjuvant therapy for resected HCC patients with microvascular invasion in a predominantly hepatitis virus cohort. The manuscript is in general well written, the study design is appropriate, and the results are presented in appropriate manner. The method section and discussion section are well drafted and presented and overall the manuscript is well written and the idea of adjuvant though not novel, the combination of two agents is novel and thus the results are interesting and significant. I have 3 major comments and 5 minor comments for authors to consider.

Reply: We appreciate the kind comments and positive feedback of the reviewer. We cherish the opportunity for the manuscript to be revised.

Specific Comments

Comment 1: 1-year overall survival of the adjuvant group was 90% and the observation group was 84% (approximately). This means that about 10-15% of patients died within 1 year. This is an important finding and needs to be included in the discussion about adjuvant therapy. There are 3 implications of these findings: (a) case selection with a possible recommendation of non-surgical options such as TACE+RFA combination if 1-year mortality can be predicted (PMID 31937433). (b) perioperative strategies to reduce surgical morbidity - especially postoperative renal and liver dysfunction/ failure (PMID 35368234) such as steroids (PMID 34621482), and (c) excluding such patients from adjuvant therapy consideration given that they are unlikely to benefit as other factors are at interplay - and excluding these patients will then increase the impact of adjuvant therapy outcomes possibly a bit more (though this needs to be proven). These issues warrant to be included in the discussion

segment. In tandem, result segment must include basic statistics of the overall cohort + PSM cohort about 30-day and 90-day mortality, bile leak rates, PHLF rates, etc.

Reply 1: Thank you very much for your precious comments. Similar 1-year OS rates after hepatectomy have been frequently reported in studies on adjuvant therapy, such as adjuvant sorafenib [1], adjuvant immune checkpoint inhibitors [2-3], and adjuvant transarterial chemoembolization [4-5]. We agree with your considerations: a) the poor prognosis of these patients may be influenced by other factors such as liver insufficiency; b) because the highly aggressive nature of the disease, such patients may not benefit from adjuvant therapy; c) excluding such patients may increase the efficacy of adjuvant therapy. Thanks for your constructive comments, we consider these comments will be helpful for our further studies. Although current studies have explored the risk factors for early death within 1 year after hepatectomy [6-8], even the phase III clinical trial, IMbrave050, did not completely avoid the occurrence of early death [9]. Combined with the references you recommend, we discussed patients at high risk of early death from three perspectives: classification, prevention, and treatment. All patients enrolled in our study needed to fulfill the criteria of no severe postoperative complications at 1 month after hepatectomy, and these are clearly described in our inclusion and exclusion criterions. In all enrolled patients, only 1 death (at 2.5 months) occurred within 90 days postoperatively. Therefore, we did not further describe the operation-related baseline statistics about 30-day and 90-day mortality, bile leak rates, PHLF rates in our paper. Thanks again for your precious comments.

References

[1] X.P. Zhang, Z.T. Chai, Y.Z. Gao, Z.H. Chen, K. Wang, J. Shi, W.X. Guo, T.F. Zhou, J. Ding, W.M. Cong, D. Xie, W.Y. Lau, S.Q. Cheng, Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: a propensity score matching analysis, HPB (Oxford). 21 (2019) 1687-1696.

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[5] Z. Wang, Z. Ren, Y. Chen, J. Hu, G. Yang, L. Yu, X. Yang, A. Huang, X. Zhang, S. Zhou, H. Sun, Y. Wang, N. Ge, X. Xu, Z. Tang, W. Lau, J. Fan, J. Wang, J. Zhou, Adjuvant Transarterial Chemoembolization for HBV-Related Hepatocellular Carcinoma After Resection: A Randomized Controlled Study, Clin. Cancer Res.. 24 (2018) 2074-2081.

[6] H. Long, C. Peng, H. Ding, Y. Zheng, J. Zhou, W. Chen, X. Zhong, Y. Shi, Y. Duan, X. Xie, M. Kuang, X. Xie, M. Lin, Predicting symptomatic post-hepatectomy liver failure in patients with hepatocellular carcinoma: development and validation of a preoperative nomogram, Eur Radiol. (2023).

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risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial, Lancet.

Changes in the text: We have added the third paragraph of "Discussion" to discuss early death within 1 year after surgery, based on the recommended references (**see Page 12, line 29**).

Comment 2: This is yet another study that shows better RFS and no impact on OS! While in general, this is an acceptable outcome, we are all very familiar that recurrent HCCs are generally asymptomatic or have no impact on liver dysfunction and physical performance of a person i.e. preventing recurrence has not had many clinical gains for a patient. It is possible that the patient might psychologically feel better, and the treating physician might also feel better; but overall, the survival is not going to be different (PMID 37431233). Even the recent IMBrave150 study showed that at 17-month follow-up, only RFS is improved and not OS. Some comments along these lines are necessary as readers should not believe that the proposed adjuvant therapy is a panacea for HCC management in the 21st century.

Reply 2: Thank you very much for your valuable comments. As you said, the present study is not the first postoperative adjuvant therapy study for HCC with significant improvement in RFS and non-significant improvement in OS [1,2]. Numerous ongoing prospective clinical studies are also only addressing RFS as the primary outcome (NCT04639180, NCT03847428, NCT05564338). Thank you for your constructive feedback. Reducing postoperative recurrence of HCC using adjuvant therapy can bring psychological comfort to patients, meanwhile, the improvement in quality of life associated with reducing probability of treatment to recurrent HCC should not be overlooked. Previous studies suggested that patients with early recurrence had worse long-term survival [3]. We found that adjuvant Camrelizumab plus Apatinib mainly reduced early recurrence after hepatectomy by Sankey diagram (as shown in the Figure S3). In fact, comparing the survival curves we see that the OS rates in the adjuvant therapy group were all better than those in the observation group before 18 months. Therefore, we considered the reasons for the non-significant improvement in

OS as follows: a) Insufficient follow-up time in the adjuvant therapy group. The number of patients willing to receive adjuvant Camrelizumab plus Apatinib has only gradually increased as Camrelizumab plus Apatinib has become more available and popularized,which caused a relative insufficient follow-up of the adjuvant treatment group; b) Patients with HCC receiving radical resection had a long natural history and were unable to have enough mortality events during the 3-year follow-up period, which resulted in a failure to reflect the differences between the observation and adjuvant treatment groups; c) Targeted therapy plus immunotherapy were allowed to use as first-line therapy for recurrent HCC patients who were not a good candidate for second radical therapy including surgery and ablation. Meanwhile, the use of Camrelizumab plus Apatinib in the adjuvant therapy group may affect the response to further treatments for patients with recurrence. For these reasons, and combined with your recommended reference, we have discussed the reasons for the significant improvement in RFS but not in OS. Thanks again for your valuable comments.

References

[1] Li SH, Mei J, Cheng Y, Li Q, Wang QX, Fang CK et al. Postoperative Adjuvant Hepatic Arterial Infusion Chemotherapy with FOLFOX in Hepatocellular Carcinoma with Microvascular Invasion: A Multicenter, Phase III, Randomized Study. J Clin Oncol 2023; 41:1898-1908.

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Changes in the text: We added a discussion in the second paragraph of "Discussion" combined with the recommended reference, as advised (**see Page 11, line 27**).

Comment 3: Line 178-180 in the statistical analysis section - please tell us which pathoclinical factors/variables were considered for PSM. These details should be provided.

Reply 3: Thank you very much for your kind comments. To eliminate differences in survival caused by differences in covariates and to ensure the independent impact of adjuvant therapy on patient survival, we performed propensity score matching (PSM) analysis of covariates that may significantly affect the survival of HCC patients after hepatectomy in previous studies, including demographic factors (age, sex), liver conditions (viral hepatitis, cirrhosis, Child-Pugh class), surgical patterns (types of hepatectomy, extent of hepatectomy), tumor characteristics (BCLC stage, tumor number, maximum tumor size, Edmondson-Steiner grade, satellite lesion), and laboratory variables (levels of AFP, ALT, AST, ALB, and TBIL). 1:2 nearest-neighbour PSM analysis with a calliper size of 0.1 resulted in SMDs of less than 0.1 for all covariates, with good comparability between the adjuvant therapy and observation groups. According to your comments, we provide detailed information about PSM analysis in the "Statistical analysis". Thanks again for your kind comments.

Changes in the text: We have modified our text as advised (**see Page 7, line 10**).

Comment 4: Please add in the result section (efficacy analysis or in the limitation section just before the conclusion) how come the median RFS and median OS were not reached in the adjuvant therapy cohort but reached in the observation cohort (both before and after PSM). Under what circumstances can this issue happen, and what can be done to prevent or reduce the risk of this happening - for example if authors had waited x months and then reported the data then could this have been avoided? Does this reduce the impact of the study results? Did you consider using this variable in PSM matching of the two groups? Would it affect the results?

Reply 4: Thank you very much for your valuable comments. It is a common situation

that survival curves failed to reach median survival time [1-2], even in numerous prospective clinical studies of adjuvant therapy [3-5]. This was caused by the insufficient events that occurred during the follow-up period. This was often attributed to insufficient follow-up time. Sufficient events did not occur during the follow-up time according to the natural course of the patient's disease. As you have suggested, prolonging the follow-up period is the most effective solution, although it will add much labor and economic consumption. We will continue to follow the enrolled patients and report the long-term survival outcomes in later works. Thanks again for your valuable comments.

References

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[5] S. Qin, M. Chen, A.L. Cheng, A.O. Kaseb, M. Kudo, H.C. Lee, A.C. Yopp, J. Zhou, L. Wang, X. Wen, J. Heo, W.Y. Tak, S. Nakamura, K. Numata, T. Uguen, D. Hsiehchen,

E. Cha, S.P. Hack, Q. Lian, N. Ma, J.H. Spahn, Y. Wang, C. Wu, P. Chow, Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial, Lancet.

Changes in the text: We have simply modified our text in the limitations as advised (**see Page 16, line 10**).

Comment 5: ICIs full form should be given along with the first use in line 274-276

Reply 5: Thank you very much for your kind suggestion. We apologize for the writing mistake. According to your comments, we have made a modification on the writing mistake. Thanks again for your kind comments.

Changes in the text: We have modified our text as advised (**see Page 11, line 3**).

Comment 6: Figures 2a and 2c shows significant improvement of RFS with adjuvant therapy with HR of 0.52 and 0.47, respectively. How does a reader interpret this? I suggest that you add 1 statement each with calculating NNT (number needed to treat) for both 2a and 2c figures. For example, the statement can read - To reduce 1 patient with HCC recurrence, xx patients need to be treated with xxx adjuvant treatment. Such simple sentences actually are more effective than numbers and statistics and help people understand better in a simple manner rather than interpreting statistics.

Reply 6: Thank you very much for your valuable suggestions. According to your comments, we calculated the NNT (number needed to treat) before and after PSM. In order to avoid impairing the brevity of Figure 2, we chose to explain the results of the NNT in the text. Thanks again for your kind suggestions.

Changes in the text: We added the results of NNT in **Figure 2**, and explained the results of NNT in the "Efficacy Analysis" section of the manuscript (**see Page 8, line 14**).

Comment 7: I know that the focus of this study is not on cost. However, it is essential that some basic costing or health economic issue is discussed in the manuscript or in

limitations. Would be good to tell local cost of therapy or injections.

Reply 7: Thanks for your constructive suggestion. The current price of camrelizumab (200 mg) is RMB¥ 2,576.64, and the price of apatinib (250 mg × 10) is RMB¥ 3,140.40. The cost for a patient to receive the entire adjuvant treatment cycle is RMB¥ 87,446.88. Obviously, this price is not acceptable to all Chinese patients, which is our limitation. However, our research results show that camrelizumab plus apatinib can effectively improve the recurrence-free survival of patients and educe the risk of recurrence by 53%, accordingly can save the cost of treatment after recurrence and improve patients' confidence. Our team is still continuing to carry out clinical trial on adjuvant targeted therapy combined with immunotherapy for resected HCC with high risk factors. We hope that in the near future, our research can support targeted combination immunotherapy to obtain indications for postoperative adjuvant therapy, so that drug combinations may be included in medical insurance, thereby reducing the financial burden on patients and truly benefiting HCC patients.

Changes in the text: No changes in the text.

Comment 8: What is the total duration of adjuvant therapy? What is the management of patients who recur after adjuvant therapy? - some details have to be given in the method section.

Reply 8: Thank you very much for your kind comments. If tumor recurrence or metastasis and intolerable toxicity do not occur, adjuvant therapy will continue until the 12th intravenous Camrelizumab. So, the total duration of adjuvant therapy is about 33 weeks. Treatments after tumor recurrence were decided by the MDT after discussion based on the patient's condition. The description has been presented in the "Interventions, follow-up, and outcomes" section of the manuscript (**see Page 5, line 24**). In order to show the management after recurrence in more detail, we have presented the results in Supplementary Material as a table. We hope that our manuscript will meet your requirements and obtain your approval. Thanks again for your kind comments.

Changes in the text: We added **Table S2** in the Supplementary Material to present

the treatments after recurrence in both groups.

Reviewer C:

General Comments

The need for adjuvant therapy for patients at high risk of recurrence after radical resection of HCC has been a matter of great academic interest and concern, which is still controversial. There is a great need for this in the clinic and among the general public, and many hospitals are implementing or conducting research in this area. However, there is currently not much high-level evidence to support adjuvant therapy after radical resection. It is most urgent to publish some credible and reliable clinical studies in a timely manner to increase the clinical basis for adjuvant treatment.

As a registered Clinical Trial, this study has also received relevant ethical approval, and its results and conclusions should be scientific and credible. The number of cases in this study is not small (although not large), and the combination of Camrelizumab and Apatinib also has Chinese characteristics. I would like to ask the authors to answer the following two additional questions.

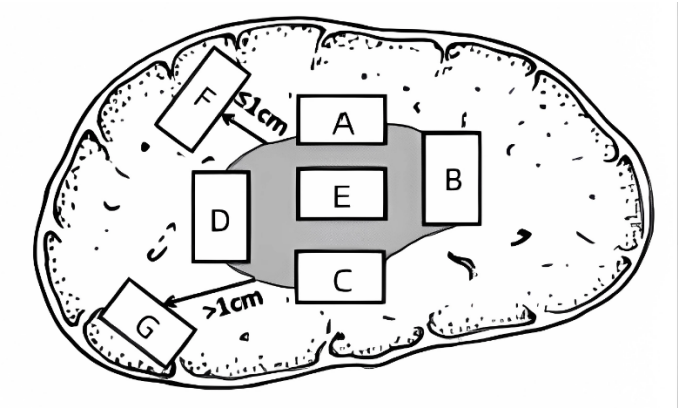
Reply: We appreciate the kind comments and positive feedback of the reviewer. We cherish the opportunity for the manuscript to be revised.

Specific Comments

Comment 1: High-risk recurrence has many meanings, and mVI positivity is just one of them. This study only focused on mVI-positive patients, and whether mVI is detected or not is closely related to the location and quantity of pathological specimens taken, as well as the level and responsibility of the pathologist. This article involves three centers. How can their pathological sampling methods and reading standards be made homogeneous?

Reply 1: Thank you very much for your precious comments. We agree with the concern you have expressed very much. Pathologic diagnoses of all patients were confirmed by pathologists with more than 5 years of professional experience. The

sampling process of all pathological specimens was strictly in accordance with the 7-point baseline sampling method prescribed by *Standard for diagnosis and treatment of primary liver cancer (2022 edition)* [1] to standardize the site and quantity of the samples taken (as shown in the figure). The diagnosis of MVI was based on the diagnostic criteria proposed by *Evidence-based practice guidelines for the standardized pathological diagnosis of primary liver cancer (2015 edition)* [2]. Of course, we do not deny the possibility that there may be false negatives in the pathologic results due to the level and responsibility of the pathologists, but all patients were enrolled in our study only after clearly MVI-positive. Thanks again for your precious comments.



References

[1] General Office of National Health Commission. Standard for diagnosis and treatment of primary liver cancer (2022 edition). J Clin Hepatol, 2022, 38 (2): 288-303.

[2] Chinese Society of Liver Cancer, Chinese Anti-Cancer Association; Liver Cancer Study Group, Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Pathology, Chinese Anti-Cancer Association et al. Evidence-based practice guidelines for the standardized pathological diagnosis of primary liver cancer (2015 edition). Chin J Hepatobiliary Surg, 2015, 21(3): 145-151.

Changes in the text: No changes in the text.

Comment 2: In the conclusion, RFS is prolonged (benefit), but OS cannot be prolonged. How to explain this? Has the relapse become more malignant?

Reply 2: Thank you very much for your valuable comments. The present study is not

the first postoperative adjuvant therapy study for HCC with significant improvement in RFS and non-significant improvement in OS [1,2]. Numerous ongoing prospective clinical studies are also only addressing RFS as the primary outcome (NCT04639180, NCT03847428, NCT05564338). We considered the reasons for the non-significant improvement in OS as follows: a) Insufficient follow-up time in the adjuvant therapy group. The number of patients willing to receive adjuvant Camrelizumab plus Apatinib has only gradually increased as Camrelizumab plus Apatinib has become more available and popularized,which caused a relative insufficient follow-up of the adjuvant treatment group; b) Patients with HCC receiving radical resection had a long natural history and were unable to have enough mortality events during the 3-year follow-up period, which resulted in a failure to reflect the differences between the observation and adjuvant treatment groups; c) Targeted therapy plus immunotherapy were allowed to use as first-line therapy for recurrent HCC patients who were not a good candidate for second radical therapy including surgery and ablation. Meanwhile, the use of Camrelizumab plus Apatinib in the adjuvant therapy group may affect the response to further treatments for patients with recurrence. In addition, for verifying whether the recurrent tumors were more malignant, we compared tumor characteristics between recurrent and non-recurrent patients. The results indicated that patients with recurrence had a higher percentage of all tumor characteristics that tended to be more malignant, and that patients with recurrence had a significantly higher percentage of BCLC B stage, multiple tumors, max size > 5 cm, and satellite lesion than patients without recurrence (as following table).

Characteristics	With Recurrence (n = 226)	Without Recurrence (n = 161)	*P*-value
BCLC Stage			<0.001
0+A	182 (80.5)	152 (94.4)	
B	44 (19.5)	9 (5.6)	
AFP (ng/ml)			0.100
≤400	133 (58.8)	108 (67.1)	
>400	93 (41.2)	53 (32.9)	
Number			<0.001
Solitary	173 (76.5)	146 (90.7)	
Multiple	53 (23.5)	15 (9.3)	
Max size (cm)			<0.001

≤5	70 (31.0)	91 (56.5)	
>5	156 (69.0)	70 (43.5)	
Edmonson tumor grade			0.092
I - II	137 (60.6)	111 (68.9)	
III - IV	89 (39.4)	50 (31.1)	
Satellite lesion			0.015
No	185 (81.9)	146 (90.7)	
Yes	41 (18.1)	15 (9.3)	

References

[1] Li SH, Mei J, Cheng Y, Li Q, Wang QX, Fang CK et al. Postoperative Adjuvant Hepatic Arterial Infusion Chemotherapy with FOLFOX in Hepatocellular Carcinoma with Microvascular Invasion: A Multicenter, Phase III, Randomized Study. J Clin Oncol 2023; 41:1898-1908.

[2] S. Qin, M. Chen, A.L. Cheng, A.O. Kaseb, M. Kudo, H.C. Lee, A.C. Yopp, J. Zhou, L. Wang, X. Wen, J. Heo, W.Y. Tak, S. Nakamura, K. Numata, T. Uguen, D. Hsiehchen, E. Cha, S.P. Hack, Q. Lian, N. Ma, J.H. Spahn, Y. Wang, C. Wu, P. Chow, Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial, Lancet.

Changes in the text: We added a discussion in the second paragraph of "Discussion" (**see Page 11, line 27**).

Response to Reviewers' and Editor's comments

Editor:

Comment 1: There is no ethical approval before starting to use "Camrelizumab plus Apatinib"? There should be sufficient evidence.

Reply 1: We cherish the opportunity for the manuscript to be revised. Thank you very much for your kind suggestion. In previous clinical trials, the combination of Camrelizumab and Apatinib showed promising efficacy and manageable safety in both first-line/second-line setting for unresected HCC and perioperative setting for resected

HCC [1-3]. Patients from Cancer Hospital, Chinese Academy of Medical Sciences were derived from clinical trial (NCT03839550), which was first presented at ESMO Asia 2019 [4]. Patients from Henan Cancer Hospital and Shandong Cancer Hospital and Institute were given adjuvant therapy as real word setting. But the therapeutic decisions of all patients were made via discussions with multidisciplinary teams. Written informed consent for treatment was obtained from all patients. This retrospective study was approved by the Institutional Review Board of each center (NO.19-010) and was registered in the Research Registry (Research Registry UIN: researchregistry9117). The study met the ethical standards for retrospective studies. Thank you again for your kind consideration.

Changes in the text: We have added the detailed "Ethical Statement" after "Footnote". (**see Page 16, line 21**)

References

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