

Peer Review File

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Reviewer A

This is a relatively large paper analyzing patients with small cell lung cancer presenting with liver metastases. Overall, this paper is well done and provides information about prognosis and factors associated with outcomes in this common clinical situation.

I have a few comments:

Comment 1: Do the authors have data why nearly 20% of patients did not receive treatment? Was it because the patient refused or due to physicians not recommending treatment? Did all of these patients have an oncology consult?

Reply: We are grateful for the suggestion. As suggested by the reviewer, we have added more details of patients did not receive treatment in our manuscript.

Changes in the text: "There were 63 patients without receiving first-line treatment, and 33 patients were provided with optimal supportive care due to inadequate organ function or poor performance status, based on the recommendation of oncologists. Additionally, 17 patients refused anti-tumor treatment, and 13 patients opted for Chinese herbal medicine treatment alone." (see Page 5, line 182-186)

Comment 2: Can the authors provide a more detailed list of what systemic therapy were used. Platinum and etoposide or Platinum + irinotecan? Other regimens? Which platinum? Was there a difference between different regimens?

Reply: Thank the reviewer for the constructive comments. we have added detailed list of first line regimens (see [etable1](#)). Most patients chose EC(n=88) or EP(n=124) as the first-line treatment. There were 25 patients receiving etoposide plus lobaplatin, which is an optional first-line treatment in China and 10 patients receiving irinotecan plus cisplatin. The regimens of NSCLC (cisplatin plus paclitaxel or gemcitabine) were adopted for 2 patients with combined SCLC. In addition, there were 9 patients with single-agent chemotherapy according to the physician's recommendation. In view of the fact that there was no differences in efficacy between EC and EP regimens in patients with ES-SCLC in previous studies (*1. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol. 2012 May 10;30(14):1692-8. 2. Azar I, Yazdanpanah O, Jang H, et al. Comparison of Carboplatin With Cisplatin in Small Cell Lung Cancer in US Veterans. JAMA Netw Open. 2022 Oct 3;5(10):e2237699.*), we did not evaluate the efficacy of these two regimens in our study. The sample sizes of the other regimens were very small, and therefore efficacy was not further assessed. Due to our single-center study, there may be bias in treatment selection, and multicenter data will be used in the future to evaluate whether different chemotherapy regimens have different efficacy in patients with ES-SCLC with Liver Metastasis. We have also added this part to the limitations of our manuscript.

Changes in the text: "Among the patients, 286 patients (81.9%) received first-line systemic therapy([etable1](#))." (see Page 5, line 176-177) and "Potential bias might have influenced treatment selection. To assess whether distinct chemotherapy regimens yield varying efficacy

in patients with extensive-stage small-cell lung cancer and liver metastasis, future research will involve the utilization of multicenter data." (see Page 9, line 362-364)

Comment 3 : Low rate of smokers – unusual in Small cell. Usually higher than 90%. This should be discussed and may limit the generalization of this to other countries where patients with SCLC are nearly all smokers.

Reply: We are grateful for the suggestion. SCLC is strongly associated with tobacco exposure. The proportion of non-smoking SCLC in Caucasians generally does not exceed 10%, but proportion of non-smoking SCLC was higher, usually in the range of 20-37% in clinical trials and observational studies from China. There were 30.4% patients with non-smoking in our study which consistent with other studies conducted in China. We also analyzed the OS of patients with smoking and non-smoking with liver metastases and found no significant difference in OS between the two groups (10.23 vs 9.73, p=0.416) (eFigure 1). For Chinese patients with ES-SCLC liver metastasis, smoking has no significant effect on prognosis, but relevant studies are needed for other races.

Changes in the text: "SCLC has strongly been associated with tobacco exposure. While the proportion of non-smokers among Caucasians with SCLC generally does not exceed 10%,^{19,20,23} the proportion of non-smokers was higher, usually in the range of 20-37%, in clinical trials and observational studies from China.^{21,22,25} There were 30.4% of non-smokers patients in our study, consistent with other studies conducted in China. We also analyzed the outcomes of SCLC cases with liver metastases who were smokers and non-smokers and found no significant difference in OS between the two groups (10.23 vs. 9.73, p=0.416) (eFigure 2). For Chinese patients with extensive-stage SCLC liver metastasis, smoking did not significantly affect prognosis, although relevant studies are warranted for other races." (see Page 8, line 301-309)

Comment 4 : What does Radiotherapy as main local treatment mean? All these patients had metastatic disease! Did this comprise consolidation thoracic radiotherapy (In the table on 19 patients received thoracic RT)? Only in patients that had residual thoracic disease or was it given for other indications? P4 line 152

Reply : Thank you for pointing this out. In addition to radiotherapy, four patients were treated with local microwave ablation of the liver, and five patients were treated with intrathoracic infusion chemotherapy. Although all patients had liver metastases at the time of diagnosis, there were 19 patients receiving thorax radiotherapy, including 13 patients with residual chest disease after first-line therapy (7 patients for PR, 6 patients for SD) and 6 patients for improving symptoms at the time of recurrence.

Comment 5 : 2nd line response to chemotherapy – can you provide platinum free interval from 1st to 2nd line therapy? What second line regimens were given? Also what 3rd line regimens were given (maybe as supplemental table).

Reply: Thank the reviewer for the constructive comments. There were 125 patients with chemotherapy-free interval of < 3 months and there were 28 patients with chemotherapy-free interval of \geq 3 months. We supplemented the 2nd and 3rd line regimens given as supplemental etable2 and etable3.

Changes in the text: Approximately 43.8% of patients received second-line treatment (etable2),

while 23.2% of patients (n=81) entered third-line treatment (etable3) (see Page 5, line 180-181)

Comment 6 : Was subsequent therapies (2nd and 3rd line) associated with improved outcomes?

Reply : This suggestion is appreciated. We added the OS of patients who received only first-line therapy, second-line therapy, and third-line therapy in the results section. Indeed, subsequent therapies (2nd and 3rd line) were associated with improved outcomes of patients with liver metastases. we have added this to the results section.

Changes in the text: "A comparison was made among patients (n=133) who exclusively received first-line treatment, those who underwent second-line treatment (n=72), and those who received third-line therapy (n=81). The median OS from diagnosis to death was 7.57 months, 10.83 months, and 16.17 months for these groups, respectively (eFigure 1). A better OS was observed for patients who received second-line treatment than those receiving first-line therapy alone, and the OS was significantly improved for those who received third-line therapy, suggesting that subsequent second and third-line therapies were associated with improved outcomes for patients with liver metastases." (see Page 6, line 236-243)

Information about liver function tests (ie blood results) in these patients may improve the study (if these are available).

Reply: Thank you very much for your question. Our study only focused on the prognosis of patients with SCLC with liver metastases and the impact of different treatment patterns on survival. It is regrettable that liver function tests were not collected in this study.

Discussion:

Comment 6 : Impower 150 study in NSCLC – not sure if this is relevant to include in the discussion as the paper is dealing with SCLC and very different to NSCLC.

Reply: Thank you very much for your reminding, we have removed this part of the discussion. Changes in the text: " There is an ongoing phase 2 study evaluating the efficacy and safety of bevacizumab in combination with chemoimmunotherapy in patients with liver metastases in extensive-stage SCLC (BELIEVE study, NCT05588388)." (see Page 9, line 352-356)

Comment 6 : General comment – some improvements in language should be made.

Reply: We apologize for poor language of our manuscript. We have now worked on language and readability and we have asked medical writing service to polish the language of the full text professionally and upload the polishing certificate.

Reviewer B

1. Line 129, please see if any reference should be cited to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 authors mentioned.

128 **Response and Outcome Evaluation**

129 The Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1, were employed
130 to assess treatment efficacy. Overall Survival 1 (OS₁) was defined as the time from the date of

Reply: Thank you, we added the corresponding references.

Changes in the text: The Response Evaluation Criteria in Solid Tumors (RECIST) criteria

version 1.1 (15). (see Page 4, line 146).

2. Tables and figures

- 1) Please capitalize the first letter of the word in each column of the Tables.
- 2) Please provide a header for the first column in Table 2.
- 3) Table 2, please indicate how data are presented in the round brackets.
- 4) Please provide a header for the second column in eTables.
- 5) Supplementary figures, please add description/unit to the X axes.

Reply: Thanks for the comments. We modified the figures and tables as required.