Peer Review File

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Point by point replies to Reviewer A:

I have read with an interest a paper entitled: Predicted Outcomes of Subdividing M1-Stage Metastatic Lung Cancer based on the Prognosis and Response of Local Consolidative Therapy. The paper is well written and easy to understand. The authors present a study evaluating proposed subtypes of M1 features and their effect on treatment and survival. This is an important idea requiring clarification. I think it does not duplicate currently published papers and as that it should be released. However, I find significant drawbacks making the study difficult to be understood. Despite the fact that authors evaluate a well-developed database (SEER) and had ambitious goals I think that the paper's quality is too low and should be corrected as a whole.

Comment 1: Despite I am not a native speaker I find significant deficits in English style. It should be corrected throughout the whole text.

Reply 1: We thank the reviewer for valuable suggestion to help us improve our manuscript. We have invited a native English speaker to help polish our article. And we hope the revised manuscript could meet the standard.

Changes in the text: We have polished our text as advised.

Comment 2: I understand that patients were diagnosed in stage IV at the moment of diagnosis and that these were not metachronous dissemination but metastasis synchronous with the primary tumor. Please state that exactly in the text.

Reply 2: We thank the reviewer for pointing out this important issue in the methods section. In this study, only patients initially diagnosed with stage IV NSCLC were included, which means that the patients enrolled in the study did not have metachronous dissemination but had multiple synchronous lesions, including metastasis synchronous with primary cancer or multiple primary lung cancer.

Changes in the text: We have added the description about this issue (see Page 4, lines 93 – 94).

Comment 3: The SEER database probably does not contain information on the differentiation between synchronous mets to the lungs and multiple primary lung cancers. Please comment on that and mention that in methods, discussion, and study limitations.

Reply 3: We thank the reviewer for pointing out this important issue. Patients presenting with more than one pulmonary nodule at the same time must fulfill strict criteria to be classified as having synchronous multiple primary lung cancer (MPLC). According to previous studies, patients with MPLC and IPM had significantly different prognosis and distinguishing between MPLC and IPM is important for guide treatment planning. (1-3)

In the current study, patients who only had one malignant primary in their lifetimes were identified utilizing the specific code “one primary only in the patient’s lifetime” in the list named as “sequence number” in the document of data description for SEER research. (4) To be more cautious, we have addressed this issue in the method section.

Changes in the text: We have added the description in methods and discussion (see Page 4, lines 93 – 94).

Comment 4: I am sorry to comment on the concept of the study but I would not name the study groups: a training set and validation set. You took two sets of randomly chosen patients. There is no training and no validation in this paper. Just a concept of analysis of two sets of patients. I can understand that it can boost the scientific soundness of the paper. Please comment on this idea. Why did you choose analysis of two sets of patients instead of analysis of twice as big a study group?

Reply 4: We thank the reviewer for pointing out this important issue and totally agree with your opinion. The initial aim of dividing the patients into a training set and a validation set was to construct a new staging system to supplement the current M1 subcategory in the training set and validate the system in the validation set. However, simply dividing a large cohort of patients into a training set or a validation set randomly cannot substantially increase the reliability of the results because of the similarity between the training and validation sets. Therefore, we decided to group the training set and validation set into a single set of 30,583 patients, and the main results changed very little.

The results of multivariate analyses and survival curves before and after regrouping the data were similar. Liver involvement was still the most important prognostic factor for cancer specific mortality (CSM). The effects of different treatments on stage IV lung cancer were also similar to the results before regrouping. Utilizing liver involvement and current M staging, the stage IV patients were divided into five groups with significant prognoses.

Changes in the text: We have deleted training set and validation set and reanalyzed all patients as single cohort (see Table 1 in the revised manuscript).

Comment 5: Lines 25-27. The methods section does not describe what the study is about. Please edit this section.

Reply 5: We thank the reviewer for pointing out this issue to help us improve our manuscript. We rewrote the methods in the abstract as follows" A total of 30,583 patients with stage IV NSCLC were identified in the Surveillance, Epidemiology, and End Results (SEER) database. To identify variables associated with increased cancer-specific mortality rates and compare the prognostic effects of different treatment strategies, a competing risk model was developed. Furthermore, prognostic factors identified by multivariate analysis were employed to supplement the current M1 subcategory. Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used to compare prognostic differences."

Changes in the text: We have added more description about this issue in methods section of abstract (see Page 2, lines 26 – 33).

Comment 6: Lines 93-98. There is repeated request for a more clear description of the study protocol and null hypothesis.

Reply 6: We thank the reviewer for pointing out this issue. The aim of distinguishing subgroups was to supplement the current M1 subcategory utilizing liver involvement, which was identified as an independent prognostic factor by multivariate analysis. Patients in group A were diagnosed with M1c NSCLC with liver involvement; patients in group B were diagnosed with M1c NSCLC without liver involvement; patients in group C were diagnosed with M1b NSCLC with liver involvement; patients in group D were diagnosed with M1b NSCLC without liver involvement; and patients in group E were diagnosed with M1a NSCLC. And the null hypothesis is that the groups divided by the current M1 subcategory and involvement of liver have no significant difference in prognosis ($p > .05$).

Changes in the text: We add more description about how to construct subgroups in the Methods part (see Page 4, lines 104 – 111).

Comment 7: Line 124. Did you take both features – male gender & histologic grade or there is SHR and 95%CI missing?

Reply 7: We thank the reviewer for careful review. We apologize for the missing status of histologic grade and male sex data. The subdistribution hazard ratios (SHRs) and 95% confidence interval (CI) of histological grade (Grade II vs. Grade I: SHR, 1.29, 95% CI, 1.17 – 1.43, $p < .001$; Grade III vs. Grade I: SHR, 1.63, 95% CI, 1.48 – 1.80, p

< *.001;* Grade IV vs. Grade I: SHR, 1.77, 95% CI, 1.52 – 2.07, $p < .001$) and male gender (SHR, 1.21; 95% CI, 1.17–1.24; $p < .001$) were added to the results part.

Changes in the text: We have added SHR, 95% CI and p values of features to the article (see Page 5, lines 137 – 140).

Comment 8: Lines 136-138 and Table 2. What does the Multivariate analysis refer to? I do not understand the explanation in the text.

Reply 8: We thank the reviewer for pointing out this issue. Utilizing a competing risk model, multivariate analysis was performed to identify prognostic factors for cancer specific mortality. To keep the information in the main body of the manuscript as concise as possible, the results of M1 division from the multivariate analysis are shown in table 2, and detailed information is shown in the supplementary materials. Since this arrangement of the results caused difficulty understanding the data, we decided to show all results of the univariate and multivariate analyses in Table 2 in the revised manuscript.

Changes in the text: To avoid misunderstanding, we have added a clear description about the method of multivariate analysis and shown all results of univariate and multivariate analyses in Table 2 in the revised manuscript (see Page 5, lines 119 – 121; Table 1 in this response letter).

Comment 9: Please exactly state the study limitations. There is more than you mentioned in the discussion.

Reply 9: We thank the reviewer for pointing out this important issue. The limitations were added.

Targeted therapy has changed the current systemic therapy landscape, especially for tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Several double-arm clinical trials demonstrated that treatment with EGFR-TKIs significantly improved progression-free survival (PFS) compared with chemotherapy. (5-7) Additionally, a phase III clinical trial showed that the first-generation ALK-TKI crizotinib significantly prolonged the PFS compared with chemotherapy in treatment-naïve patients. In addition, immunotherapy has also substantially changed the current systemic therapy landscape a lot. For patients with tumor programmed cell death ligand 1 (PD-L1) expression of 50% or higher, pembrolizumab or atezolizumab monotherapy improved OS compared to doublet chemotherapy. (8) In another trial, pembrolizumab plus chemotherapy significantly improved survival of patients with metastatic nonsquamous NSCLC without EGFR or ALK mutations (9) and patients with previously untreated metastatic, squamous NSCLC (10). A survival benefit of atezolizumab plus chemotherapy and bevacizumab was also observed in patients with PD-L1-unselected advanced nonsquamous NSCLC. (11)

However, the SEER database cannot provide specific codes for mutation status, targeted therapy information, and immunotherapy status. We have added relevant information to the revised manuscript.

Changes in the text: We have discussed and added the limitations in the revised manuscript (see Page 9, lines 232 – 241; Page 10, lines 263 – 265).

Comment 10: What were the methods for the assumption of CSM?

Reply 10: We thank the reviewer for careful review. In our article, CSM (cancer-specific mortality) was identified using the specific code "SEER CAUSE-SPECIFIC DEATH CLASSIFICATION" provided by the SEER database as in prior articles. (12,13) "Dead (attributable to this cancer dx)" in this column indicates death due to lung cancer.

Changes in the text: We add the specific description about how to identify CSM (see Page 5, lines 114 – 115).

Comment 11: I do not find the information on how many patients were lost to follow-up. What is the median follow-up? What was the method of assessment of follow-up?

Reply 11: We thank the reviewer for pointing out these important issues. First, the last follow-up time of the patients analyzed in the current study was the December of 2019. In total, 1,328 patients were lost to follow-up and censored. Then, the median follow-up of the whole cohort was calculated to be 23.0 (95% confidence interval [CI], 22.4 – 23.6) months.

The Surveillance, Epidemiology, and End Results (SEER) database is a program regulated by the National Cancer Institute (NCI), and the follow-ups of the SEER database are performed by hospital-based and many population-based registries each

month. The governing body or cancer committee determines the sequence of contacts or governing body for follow-up. The appropriate physician must give permission to contact patients or relatives directly.

1) If a patient returns to the facility, records are obtained and appropriate information is extracted. 2) If a patient does not return to the institution, follow-up letters are usually mailed to the managing or referring physician. If physicians have not seen a patient since the date of last contact, follow-up letters are then usually sent to the patient, family members, or other contacts. 3) If a response is not received, letters are mailed to new sources until all potential sources have been exhausted.

Follow-up procedures vary with different software systems. Letters can be generated individually or in a batch depending on the software. Attempts should be made periodically to contact all patients who do not have a current follow-up including those considered lost to follow-up.(14)

Changes in the text: We add the median follow-up time in results (see Page 5, lines 129 – 131).

Comment 12: What was the type of the surgeries performed? If detailed data would make the paper too complicated please comment on that in the text. Please state if the surgeries were curative?

Reply 12: We thank the reviewer for pointing out this important issue. As shown in Table 2 in this response letter, a total of 1213 patients received surgical treatment, with 531 and 682 patients in the surgery-only group and chemotherapy plus surgery group,

respectively. Among these 1213 patients, the primary tumor was treated surgically in 1204 patients, the primary tumor and distant sites were treated surgically in 165 patients, and the primary tumor and regional sites were treated surgically in 28 patients. The most common surgical approach was lobectomy (558 patients, 46.0%), followed by wedge resection (381 patients, 31.4%). All surgeries were performed as local consolidative therapy.

Changes in the text: There is no changes in the text.

Comment 13: Did the patients receive molecularly driven chemotherapeutics?

Reply 13: Thank the reviewer for pointing out this important issue. Targeted therapy has been proved to improve prognosis of NSCLC patients with specific mutations of genes including EGFR and ALK in prior studies. (7,15-17) However, there are no record of gene mutation status or targeted therapy in SEER database, which is also an important limitation addressed in the limitation section.

Besides, 17,075 patients received chemotherapy in the current study with 16,393 and 682 patients receiving chemotherapy only and chemotherapy plus surgery, respectively.

Changes in the text: We have added this issue to the limitations (see Page 10, lines 263 – 265).

Comment 14: You mention that you explained that the information about the missing data is explained in lines 87-90. I do not find enough information in this part of the text.

Reply 14: We thank the reviewer for pointing out this important issue. A total of 12,648 patients were excluded because NSCLC was not the first or only cancer, 96,332 patients were excluded for having tumors that were not stage IV, 24,381 patients were excluded due to unknown histologic grades, 4,301 patients were excluded because of unknown bone, brain, liver or lung involvement, 2,719 patients were excluded because of unknown demographic characteristics, and 1,920 patients were excluded due to unknown treatment modalities. Detailed statuses are also shown in Figure 1 in the revised manuscript and this response letter.

Changes in the text: We have added the detailed information in the Figure 1 in the revised manuscript (see Figure1 in this response letter and the revised manuscript).

Comment 15: Line 29: please extend the SHR abbreviation.

Reply 15: Thank reviewer for careful reading. We feel sorry for this mistake. And subdistribution hazard ratio, as abbreviation of SHR has been added to the mentioned part.

Changes in the text: We have extended the SHR abbreviation (see Page 2, line 35).

Comment 16: Table 1. Marital status: none – you mean single or missing data?

Reply 16: We thank the reviewer for pointing out this issue. “Married” means married (including common law) and “none” means single (never married), separated, divorced or widowed according to the data description document for SEER research. (4) To avoid misunderstanding, we replaced “none” with “others”.

Changes in the text: We replaced “none” of marital status with “others” (see Table 1 and Table 2 in the revised manuscript).

Point by point replies to Reviewer B:

The authors have demonstrated prognosis of locally advanced lung cancer using large-scale data according to the metastasis status. However, there seems to be a part that needs to be more clarified.

Comment 1: In the abstract, the group was divided into 5 groups, but only the results are shown without a specific definition for this.

You need to explain the groups.

Reply 1: We thank the reviewer for pointing out this issue. We feel sorry for loss of definition for subgroups. To supplement current M1 subcategory, subgroups were constructed based on M1 subcategory and involvement of liver which was identified as the most prognostic factor in multivariate analysis. Patients in group A were diagnosed with M1c NSCLC with liver involvement; patients in group B were diagnosed with M1c NSCLC without liver involvement; patients in group C were diagnosed with M1b NSCLC with liver involvement; patients in group D were diagnosed with M1b NSCLC without liver involvement; and patients in group E were diagnosed with M1a NSCLC.

Changes in the text: We have added the description of subgroup construction in method section (see Page 2, lines 38 – 40).

Comment 2: In M1c, if liver inv is present, the prognosis is not worse?

Reply 2: We thank the reviewer for pointing this issue out. The description "A vs. B" means M1c disease with liver involvement vs. M1c disease without liver involvement, with M1c disease without liver involvement serving as the reference. Therefore, patients with liver involvement had a worse prognosis in the M1c stage (A vs. B: SHR, 1.363, 95% CI, 1.300-1.429, $p < 0.001$). For clarity, we added a new figure in the revised manuscript (Figure 4) and this response letter (Figure 2) comparing cancer-specific mortality among these 5 groups.

Changes in the text: We have added a description "A vs. B means B as reference" (see Figure 4 in the revised manuscript).

Comment 3: Patients who underwent surgery and chemotherapy are expected to have a lower tumor burden, and the patient's ECOG is also expected to be better. As a result, don't you think this group has lived longer than the others?

Reply 3: We thank the reviewer for pointing out this important issue. We compared clinicopathological statuses between patients with different treatment modalities (see Table 3 in this response letter). A total of 12977, 16924, and 682 patients who received no therapy, surgery or chemotherapy only, and surgery plus chemotherapy, respectively. Compared to patients who received chemotherapy or surgery only, patients received combined therapy had a lower tumor burden (T stage, $p = 0.038$; N stage, $p < 0.001$; M stage, $p < 0.001$) and the ECOG scores were absent in the SEER database. This bias

may influence the prognosis of patients. Therefore, we conducted a propensity-score matching analysis. As shown in Table 4 in this response letter, the baseline characteristics did not significantly differ between patients receiving surgery plus chemotherapy and those receiving chemotherapy or surgery alone. Survival curves demonstrated that patients receiving surgery plus chemotherapy had a significantly better prognosis than patients receiving chemotherapy or surgery only after balancing baseline characteristics (see Figure 3 in this response letter).

In addition, a recent randomized controlled clinical trial, in which no significant difference in ECOG scores was observed between the chemotherapy only group and the local consolidative therapy plus chemotherapy group, demonstrated that local consolidative therapy could prolong overall survival and progression-free survival in patients with oligometastatic NSCLC compared to chemotherapy only, which confirmed the results of the current study. (18) Similar results were also observed in several studies, including a small clinical trial and a propensity-score matching analysis. (19-21) To be cautious, we have discussed the above information in the discussion section and addressed the absence of ECOG scores in the limitations section.

Changes in the text: We have addressed the issues in the discussion and particular limitations (see Page 8, lines 206 – 216; Page 10, lines 263 – 265).

Comment 4: Similarly, patients with surgery or chemotherapy alone are considered to have better performance status and less tumor burden than patients with only conservative care.

Reply 4: We thank the reviewer for pointing out this important issue. As shown in Table 3 in this response letter, patients receiving only conservative care had a lower N stage ($p < 0.001$) but a higher rate of liver involvement ($p < 0.001$). T stage ($p = 0.084$), M stage ($p = 0.563$), and rates of bone involvement ($p = 0.523$) and brain involvement ($p = 0.275$) were comparable between patients receiving conservative care and those receiving chemotherapy or surgery alone.

To be cautious, we conducted a propensity-score matching (PSM) analysis. As shown in Table 5 in this response letter, baseline characteristics did not significantly differ between patients receiving conservative care and those receiving chemotherapy or surgery alone. Survival curves demonstrated that patients receiving chemotherapy or surgery only had a significantly better prognosis than patients receiving conservative care after balancing baseline characteristics (see Figure 4 in this response letter). Based on these results, we think that patients can significantly benefit from surgery or chemotherapy alone compared with conservative care even though a lower tumor burden was observed in patients receiving conservative care.

Changes in the text: There is no changes in the text.

Comment 5: In M1a of Figure 3, the surgery alone group has a better survival rate than the surgery+chemo group in the future. How should this be interpreted?

Reply 5: We thank the reviewer for pointing out this important issue. As a retrospective study, the selection bias cannot be ignored, which may influence the results of this part. What' more, the 95% confidence intervals of survival curves intersected and the results

of the multivariate analysis also showed that combination therapy was not a significant prognostic factor compared with surgery only (SHR, 0.789; 95%CI, 0.610-1.021, p = 0.072). In addition, the relatively smaller numbers of patients in these two groups compared to those in the other groups also may have also generated such results, with 267 patients in the surgery only group and 266 patients in the combination therapy group.

Changes in the text: There is no changes in the text.

Point by point replies to Reviewer C:

In this manuscript, Wang et al. studied prognostic variables in a large cohort of advanced NSCLC patients using SEER database to subclassify M1 disease into distinct subgroups based upon survival. They found that liver, brain and number of lesions are significantly associated with OS and proposed a classification in 5 groups based on liver involvement and M1 descriptor. In this regard, the authors basically complemented the 8th TNM Edition (M1a/b/c) taking into consideration liver involvement which is a well known prognostic factor in lung cancer.

The manuscript is interesting but has several issues that should be addressed:

Comment 1: In the introduction, the following sentence is a bit misleading: “For patients with stage M1 disease, systemic therapy is the main strategy, whether it involves chemotherapy, immune therapy, or targeted therapy, and local therapy tends to

be selected or reserved for palliative cases". I would suggest using stage IV instead of stage M1 and I do not understand the statement about local therapy in palliative cases. Could the authors clarify this?

Reply 1: We thank the reviewer for pointing this issue and apologize for this expression. We have rewritten this sentence as follows "For patients with stage IV disease, systemic therapy including chemotherapy, immune therapy, and targeted therapy is the main strategy and local consolidative therapy tends to be performed for patients with oligometastases."

Changes in the text: We have rewritten this part of text (see Page 3, lines 62 – 64).

Comment 2: In all the manuscript, the authors utilize the term locally advanced NSCLC, however this work focuses on stage IV NSCLC with especial interest on oligometastatic disease.

Reply 2: We thank the reviewer for professional suggestion and totally agree with you. We have replaced "locally advanced NSCLC" with "stage IV" in the revised manuscript.

Changes in the text: We have replaced "locally advanced NSCLC" with "stage IV NSCLC" in the revised manuscript.

Comment 3: In Table 2 the authors showed that patients were well balanced among group 1 &2 in terms of clinicopathological characteristics. Were they also balanced according to tobacco history and histological type (squamous vs nonsquamous)? In this regard, adenocarcinoma histology was significantly associated with overall survival in

the metanalysis conducted by Answorth et al. IJROBP 2014 (doi: 10.1016/j.ijrobp.2014.08.028).

Reply 3: We thank the reviewer for pointing out this issue. According to the first Reviewer's opinion, we gave up dividing patients into a training set (group 1) and a validation set (group 2) and analyzed all 30,583 patients as a whole set. Tobacco history and histological type were reported to have an impact on the prognosis of patients with NSCLC in several prior studies.(22-26) However, the SEER database lacks tobacco status, and we cannot compare tobacco status between groups. To be cautious, we have addressed this issue in the limitations.

For histological type, we divided patients into adenocarcinoma, squamous cell carcinoma and others according to the specific codes from SEER database. (4) 6,802, 18,785 and 4,996 patients were diagnosed with squamous cell carcinoma, adenocarcinoma and others, respectively. The results of the multivariate analysis demonstrated that histological type was an independent prognostic factor for CSM (adenocarcinoma vs. squamous cell carcinoma, SHR: 0.853, 95% CI: 0.825 – 0.881, $p < 0.001$; others vs. squamous cell carcinoma, HSR: 1.004, 95% CI: 0.963 – 1.046, $p = 0.860$). Adenocarcinoma was associated with a better prognosis.

Besides, we thank the reviewer for reminding us the paper published by Answorth and his colleagues. We have read and cited this review in the revised manuscript.

Changes in the text: We have added histological type of patients in the revised manuscript and addressed the absence of smoking status in the limitations (see Page 10, lines 263 – 265; Table 1 and Table 2 in the revised manuscript).

Comment 4: In the multivariate analysis, bone and brain involvement as well as N involvement were significantly associated with overall survival as shown in Supplem. Table 3. In the Answorth metanalysis N-stage was also predictive of overall survival. It is not clear why those variables (bone/brain/mediastinal involvement) were not considered in the proposed groups based on independent prognostic factors.

Reply 4: We thank the reviewer for pointing this important issue out. Utilizing multivariate analysis, N stage (N1 vs. N0: SHR, 1.190, 95%CI, 1.129-1.255, $p < 0.001$; N2 vs. N0: SHR, 1.307, 95%CI, 1.264-1.352, $p < 0.001$; N3 vs. N0: SHR, 1.400, 95%CI, 1.344-1.458, $p < 0.001$), involvement of bone (SHR, 1.281, 95%CI, 1.240-1.324, $p < 0.001$), involvement of brain (SHR, 1.234, 95%CI, 1.193-1.277, $p < 0.001$), and involvement of liver (SHR, 1.470, 95%CI, 1.414-1.528, $p < 0.001$) were observed to have a significant impact on the prognosis of patients with stage IV NSCLC. Then, liver involvement, which had the highest SHR value of 1.470, was employed to supplement the current M1 subcategory.

The original aim was to supplement the M1 subcategory, and the mediastinal metastasis was identified the by N stages of N2 and N3, which means that the N stage is utilized to evaluate the M stage and that the role of N stage is overestimated. Brain involvement and bone involvement had lower SHR values (1.223 for brain; 1.281 for bone) than liver involvement (SHR as 1.470). To create a concise model that is convenient for clinical practice, we only used liver involvement to implement the M1 subcategory.

Changes in the text: There is no changes in the text.

Comment 5: The authors found that patients who received surgery plus chemo had better outcome than those treated with surgery or chemo only. However, these results could be biased since patients who received surgery plus chemo would probably have better functional status, organic function and lower tumor volume. Could the authors compare the patients characteristics of patients who receive more intensive treatment with those who only did surgery or chemotherapy?

Reply 5: We thank the reviewer for pointing out this important issue. We compared clinicopathological statuses between patients with different treatment modalities (see Table 3 in this response letter). A total of 12977, 16924, and 682 patients who received no therapy, surgery or chemotherapy only, and surgery plus chemotherapy, respectively. Compared to patients who received chemotherapy or surgery only, patients received combined therapy had a lower tumor burden (T stage, $p = 0.038$; N stage, $p < 0.001$; M stage, $p < 0.001$) and the ECOG scores were absent in the SEER database. This bias may influence the prognosis of patients. Therefore, we conducted a propensity-score matching analysis. As shown in Table 4 in this response letter, the baseline characteristics did not significantly differ between patients receiving surgery plus chemotherapy and those receiving chemotherapy or surgery alone. Survival curves demonstrated that patients receiving surgery plus chemotherapy had a significantly better prognosis than patients receiving chemotherapy or surgery only after balancing baseline characteristics (see Figure 3 in this response letter).

In addition, a recent randomized controlled clinical trial, in which no significant difference in ECOG scores was observed between the chemotherapy only group and the local consolidative therapy plus chemotherapy group, demonstrated that local consolidative therapy could prolong overall survival and progression-free survival in patients with oligometastatic NSCLC compared to chemotherapy only, which confirmed the results of the current study. (18) Similar results were also observed in several studies, including a small clinical trial and a propensity-score matching analysis. (19-21) To be cautious, we have discussed the above information in the discussion section and addressed the absence of ECOG scores in the limitations section.

Changes in the text: There is no changes in the text.

Comment 6: In the discussion the authors mentioned that "chemotherapy may potentiate the effects of systemic therapy" which seems a bit redundant and confusing.

Reply 6: We thank the reviewer for pointing out this important issue and apologize for the inconsistent description. Chemotherapies have been reported to enhance the antitumor response and improve the prognosis of patients through multiple mechanisms including the induction of immunogenic cell death. (27,28) We have rewritten this sentence as follows "Second, certain chemotherapies have been reported to enhance antitumor immune responses and may improve the prognosis of patients."

Changes in the text: We have rewritten this sentence. (See Page 8, lines 223 – 225)

Comment 7: When the authors mentioned that aggressive treatment for patients with oligometastatic stage IV lung cancer is associated with a favorable outcome, they should mention and discuss the results of two important randomized phase II clinical trials in this setting: Gómez et al. JCO 2019 (doi: 10.1200/JCO.19.00201), Iyengar et al. JAMA Oncol 2018 (doi: 10.1001/jamaoncol.2017.3501).

Reply 7: We thank the reviewer for the professional suggestion and totally agree with the reviewer. Only a small proportion of patients with oligometastatic NSCLC could have long-term disease-free intervals. Local consolidative treatment, including surgery and radiation, improved the overall survival of these patients in several retrospective studies. (26,29,30) Furthermore, several prospective phase II clinical trials also suggested improved progression-free survival with local consolidative therapy including surgery and stereotactic body radiation therapy (SBRT) for patients with oligometastatic NSCLC (18,31,32) Recently, a meta-analysis including 943 patients reported that 95% of patients with oligometastatic cancer who received surgery and SBRT had local control at one year. (33) In this article, we also demonstrate that chemotherapy plus surgery can improve the survival of stage IV patients, which strengthens the prognostic impact of local consolidative therapy.

Changes in the text: We have added the discussion about these two articles in the revised manuscript (see Page 8, lines 206 – 216).

Comment 8: The authors commented the limitations of the study but they should discuss further that the current systemic treatment landscape has evolved and many

patients received immunotherapy alone or combined with chemotherapy, which may have great impact on the natural history of the disease especially in patients with lower tumor burden (M1a & M1b).

Reply 8: We thank the reviewer for the professional suggestion and totally agree with the reviewer. Platinum-based chemotherapy used to be first-line therapy for advanced NSCLC that lacks targetable mutations. However, immunotherapy has changed the current systemic therapy landscape. For patients with tumor programmed cell death ligand 1 (PD-L1) expression of 50% or higher, pembrolizumab or atezolizumab monotherapy improved OS versus doublet chemotherapy. (8) In another trail, pembrolizumab plus chemotherapy significantly improved survival of patients with metastatic non-squamous NSCLC without EGFR or ALK mutations (9) and patients with previously untreated metastatic, squamous NSCLC (10). Survival benefit of atezolizumab plus chemotherapy and bevacizumab was also observed in patients with PD-L1-unselected, advanced, non-squamous NSCLC. (11)

Changes in the text: We have discussed about this part and added it to the limitations (see Page 9, lines 232 – 241; Page 10, lines 263 – 265).

Comment 9: Why one of the conclusions was not previously mentioned in the results (M1a patients with VPI, combined therapy including chemotherapy and surgery is the best choice)?

Reply 9: We thank the reviewer for pointing out this important issue and apologize for the absence of this result in the results section. The initial aim of this part was to select

patients with certain clinical characteristics who can benefit most from combined therapy. However, the presence of VPI only has limited value of guiding treatment for stage IV NSCLC. Besides, the evidence for this part is weak. Therefore, we decided to delete this part from the results and conclusion sections.

Changes in the text: We have deleted this part in the result and conclusion sections.

Comment 10: The manuscript contains several typographical errors that should be corrected (e.g. caption of table 3).

Reply 10: We thank the reviewer for reminding us. And we have corrected these typographical mistakes.

Changes in the text: We have rearranged Table 3 and corrected the typographical errors.

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small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
7. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
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Table 1. Univariate and Multivariate Analysis of Cancer-Specific Mortality in Whole Set

	Univariate Analysis		Multivariate Analysis	
	SHR (95%CI)	P Value	SHR (95%CI)	P Value
Age	1.016(1.015-1.017)	<0.001	1.010(1.008-1.011)	<0.001
Sex				
Female	Reference		Reference	
Male	1.243(1.211-1.276)	<0.001	1.206(1.174-1.239)	<0.001
Race/Ethnicity				
Black	Reference		Reference	
Other	0.677(0.639-0.718)	<0.001	0.709(0.668-0.752)	<0.001
White	0.991(0.955-1.029)	0.644	1.022(0.984-1.061)	0.268
Marital status				
Married	Reference		Reference	
Others	1.181(1.151-1.212)	<0.001	1.082(1.053-1.111)	<0.001
Histological type				
Squamous cell carcinoma	Reference		Reference	
Adenocarcinoma	0.750(0.727-0.774)	<0.001	0.853(0.825-0.881)	<0.001
Others	0.968(0.930-1.008)	0.116	1.004(0.963-1.046)	0.860
Histologic Grade				
Well differentiated; Grade I	Reference		Reference	
Moderately differentiated; Grade II	1.397(1.263-1.546)	<0.001	1.292(1.167-1.431)	<0.001
Poorly differentiated; Grade III	1.880(1.706-2.071)	<0.001	1.630(1.478-1.798)	<0.001

Undifferentiated; anaplastic; Grade IV	2.041(1.749-2.380)	<0.001	1.774(1.520-2.071)	<0.001
T classification				
T1a	Reference		Reference	
T1b	0.986(0.846-1.149)	0.858	0.922(0.791-1.075)	0.299
T1c	1.063(0.916-1.233)	0.420	0.983(0.847-1.141)	0.824
T2a	1.181(1.024-1.363)	0.022	1.104(0.957-1.274)	0.176
T2b	1.401(1.211-1.621)	<0.001	1.230(1.063-1.424)	0.006
T3	1.339(1.161-1.543)	<0.001	1.236(1.072-1.426)	0.004
T4	1.359(1.179-1.565)	<0.001	1.252(1.086-1.444)	0.002
N classification				
N0	Reference		Reference	
N1	1.147(1.089-1.209)	<0.001	1.190(1.129-1.255)	<0.001
N2	1.274(1.233-1.316)	<0.001	1.307(1.264-1.352)	<0.001
N3	1.258(1.210-1.309)	<0.001	1.400(1.344-1.458)	<0.001
M classification				
M1a	Reference		Reference	
M1b	1.261(1.220-1.304)	<0.001	1.209(1.162-1.257)	<0.001
M1c	1.625(1.567-1.685)	<0.001	1.348(1.274-1.427)	<0.001
Bone Involved				
No	Reference		Reference	
Yes	1.266(1.233-1.300)	<0.001	1.281(1.240-1.324)	<0.001
Brain Involved				
No	Reference		Reference	
Yes	1.114(1.083-1.147)	<0.001	1.234(1.193-1.277)	<0.001
Liver Involved				
No	Reference		Reference	
Yes	1.536(1.486-1.587)	<0.001	1.470(1.414-1.528)	<0.001
Lung Involved				
No	Reference			

Yes	0.999(0.972-1.027)	0.951		
Treatment				
None	Reference		Reference	
Surgery Only	0.276(0.246-0.309)	<0.001	0.383(0.341-0.430)	<0.001
Chemo Only	0.374(0.364-0.384)	<0.001	0.373(0.362-0.383)	<0.001
Chemo + Surgery	0.183(0.163-0.803)	<0.001	0.227(0.203-0.254)	<0.001

Abbreviations: Chemo, chemotherapy; CI, confidence interval; SHR, subdistribution hazard ratio.

Table 2. Surgical approach of patients.

	Surgery Only (531)	Chemo plus Surgery (682)	Total (1213)
Pneumonectomy	37(7.0)	33(4.8)	70(5.8)
Lobectomy	241(45.4)	317(46.5)	558(46.0)
Sublobar resection	10(1.9)	17(2.5)	27(2.2)
Segmentectomy	22(4.1)	20(2.9)	42(3.5)
Wedge resection	173(32.6)	208(30.5)	381(31.4)
Bronchial sleeve resection	4(0.8)	2(0.3)	6(0.5)
Local tumor destruction	44(8.3)	85(12.5)	129(10.6)

Table 3. Baseline Characteristics Stratified by Treatment Modality

	Whole Cohort	No Therapy	Chemo or Surgery Only	Chemo + Surgery	p_1 value	p_2 value	p_3 value
Total	30583	12977	16924	682			
Age, Mean ± SD	67.1±11.2	70.3±11.0	64.8±10.6	61.4±10.9	< 0.001	< 0.001	< 0.001
Sex					< 0.001	0.407	< 0.001
Female	13697(44.8)	5580(43.0)	7792(46.0)	325(47.7)			
Male	16886(55.2)	7397(57.0)	9132(54.0)	357(52.3)			
Race, No. (%)					0.917	0.680	0.908
Black	4169(13.6)	1091(14.6)	2182(12.9)	86(12.6)			
Other	2762(9.0)	1012(7.8)	1685(10.0)	65(9.5)			
White	23652(77.3)	10064(77.6)	13057(77.1)	531(77.9)			
Marital status, No. (%)					< 0.001	0.052	< 0.001
Married	16153(52.8)	5815(44.8)	9913(58.6)	425(62.3)			
Unmarried	14430(47.2)	7162(55.2)	7011(41.4)	257(37.7)			
Histological type					< 0.001	0.907	< 0.001
Squamous cell carcinoma	6802(22.2)	3315 (25.5)	3354 (19.8)	133 (19.5)			
Adenocarcinoma	18785(61.4)	7386 (56.9)	10955 (64.7)	444 (65.1)			
Others	4996(16.3)	2276 (17.5)	2615 (15.5)	105 (15.4)			
Histologic Grade, No. (%)					< 0.001	< 0.001	< 0.001

Well differentiated; Grade I	1669(5.5)	638(4.9)	968 (5.7)	63(9.2)			
Moderately differentiated; Grade II	8663(28.3)	3506 (27.0)	4911 (29.0)	246 (36.1)			
Poorly differentiated; Grade III	19551(63.9)	8555 (65.9)	10630 (62.8)	366(53.7)			
Undifferentiated; anaplastic; Grade IV	700(2.3)	278 (2.2)	415 (2.5)	7(1.0)			
Pathologic T stage, No. (%)					0.084	0.038	0.014
T1a	284(0.9)	120(0.9)	157(0.9)	7(1.0)			
T1b	1415(4.6)	543(4.2)	834(4.9)	38(5.6)			
T1c	2129(7.0)	867(6.7)	1220(7.2)	42(6.2)			
T2a	5721(18.7)	2404(18.5)	3155(18.6)	162(23.8)			
T2b	2689(8.8)	1183(9.1)	1466(8.7)	40(5.9)			
T3	8022(26.2)	3467(26.7)	4364(25.8)	191(28.0)			
T4	10323(33.8)	4393(33.9)	5728(33.8)	202(29.6)			
Pathologic N stage, No. (%)					< 0.001	<0.001	< 0.001
N0	7535(24.6)	3604(27.8)	3650(21.6)	281(41.2)			
N1	2535(8.3)	1052(8.1)	1392(8.2)	91(13.3)			
N2	14366(47.0)	6126(47.2)	7988(47.2)	252(37.0)			
N3	6147(20.1)	2195(16.9)	3894(23.0)	58(8.5)			
Pathologic M stage, No. (%)					0.563	<0.001	< 0.001
M1a	7520(24.6)	3237(24.9)	4017(23.7)	266(39.0)			

M1b	14517(47.5)	6012(46.3)	8158(48.2)	347(50.9)			
M1c	8546(27.9)	3728(28.7)	4749(28.1)	69(10.1)			
Involvement of bone, No. (%)					0.523	< 0.001	< 0.001
No	19037(62.2)	8046(62.0)	10432(61.6)	559(82.0)			
Yes	11546(37.8)	4931(38.0)	6492(38.4)	123(18.0)			
Involvement of brain, No. (%)					0.275	0.758	0.497
No	22097(72.3)	9332(71.9)	12267(72.5)	498(73.0)			
Yes	8486(27.7)	3645(28.1)	4657(27.5)	184(27.0)			
Involvement of liver, No. (%)					< 0.001	< 0.001	< 0.001
No	25311(82.8)	10562(81.4)	14112(83.4)	634(93.4)			
Yes	5272(17.2)	2415(18.6)	2812(16.6)	45(6.6)			

Abbreviations: Chemo, chemotherapy. P_1 was estimated between no therapy group and chemotherapy or surgery only group. P_2 was estimated between chemotherapy or surgery only group and combination group. P_3 was estimated among three groups.

Table 4. Baseline characteristics of patients who received surgery plus chemotherapy and chemotherapy or surgery only after propensity-score matching.

	Chemo or Surgery Only	Chemo plus Surgery	p value
Total	2031	677	
Age, Mean ± SD	61.6 ± 10.7	61.8 ± 10.9	0.659
Sex			0.947
Female	960(47.3)	321(47.4)	
Male	1071(52.7)	356(52.6)	
Race, No. (%)			0.513
Black	284(14.0)	86(12.7)	
Other	185(9.1)	63(9.3)	
White	1562(76.9)	528(78.0)	
Marital status, No. (%)			0.982
Married	1267(62.4)	422(62.3)	
Unmarried	764(37.6)	255(37.7)	
Histological type			0.771
Squamous cell carcinoma	418 (20.6)	133 (19.6)	
Adenocarcinoma	1297(63.9)	440 (65.0)	
Others	316(15.6)	104 (15.4)	
Histologic Grade, No. (%)			0.660
Well differentiated; Grade I	189 (9.3)	61 (9.0)	
Moderately differentiated; Grade II	725 (35.7)	242 (35.8)	
Poorly differentiated; Grade III	1100 (54.2)	367 (54.2)	
Undifferentiated; anaplastic; Grade IV	17 (0.8)	7 (1.0)	
Pathologic T stage, No. (%)			0.926
T1a	17 (0.8)	7 (1.0)	
T1b	109 (5.4)	38 (5.6)	
T1c	143 (7.0)	42 (6.2)	
T2a	460 (22.6)	162 (23.9)	
T2b	125 (6.2)	40 (5.9)	

T3	584 (28.8)	188 (27.8)	
T4	593 (29.2)	200 (29.5)	
Pathologic N stage, No. (%)			0.713
N0	814 (40.1)	278 (41.1)	
N1	272 (13.4)	89 (13.1)	
N2	772 (38.0)	252 (37.2)	
N3	173 (8.5)	58 (8.6)	
Pathologic M stage, No. (%)			0.374
M1a	747 (36.8)	261 (38.6)	
M1b	1062 (52.3)	347 (51.3)	
M1c	222 (10.9)	69 (10.2)	
Involvement of bone, No. (%)			0.399
No	1632 (80.4)	554 (81.8)	
Yes	399 (19.6)	123 (18.2)	
Involvement of brain, No. (%)			1.000
No	1479 (72.8)	493 (72.8)	
Yes	552 (27.2)	184 (27.2)	
Involvement of liver, No. (%)			0.727
No	1888 (93.0)	632 (93.4)	
Yes	143 (7.0)	45 (6.6)	
Involvement of lung, No. (%)			0.718
No	1535 (75.6)	507 (74.9)	
Yes	496 (24.4)	170 (25.1)	

Table 5. Baseline characteristics of patients who received no therapy and chemotherapy or surgery only after propensity-score matching.

	Surgery Only	Chemo or Surgery Only	p value
Total	10857	10857	
Age, Mean ± SD	68.3 ± 10.5	68.1 ± 9.8	0.183
Sex			0.511
Female	6214(57.2)	6166(56.8)	
Male	4643(42.8)	4691(43.2)	
Race, No. (%)			0.943
Black	1550(14.3)	1536(14.1)	
Other	913(8.4)	906(8.3)	
White	8394(77.3)	8415(77.5)	
Marital status, No. (%)			0.674
Married	5457(50.3)	5488(50.5)	
Unmarried	5400(49.7)	5369(49.5)	
Histological type			0.541
Squamous cell carcinoma	2541(23.4)	2507 (23.1)	
Adenocarcinoma	6470(59.6)	6548 (60.3)	
Others	1846(17.0)	1802 (16.6)	
Histologic Grade, No. (%)			0.990
Well differentiated; Grade I	566 (5.2)	529 (4.8)	
Moderately differentiated; Grade II	2937 (27.1)	2982 (27.5)	
Poorly differentiated; Grade III	7105 (65.4)	7109 (65.5)	
Undifferentiated; anaplastic; Grade IV	249 (2.3)	237 (2.2)	
Pathologic T stage, No. (%)			0.632
T1a	102 (0.9)	101 (0.9)	
T1b	486 (4.5)	491 (4.5)	
T1c	749 (6.9)	775 (7.1)	
T2a	2013 (18.5)	2030 (18.7)	
T2b	972 (9.0)	982 (9.0)	

T3	2851 (26.3)	2818 (26.0)	
T4	3684 (33.9)	3660 (33.7)	
Pathologic N stage, No. (%)			0.910
N0	2704 (24.9)	2704 (24.9)	
N1	890 (8.2)	877 (8.1)	
N2	5220 (48.1)	5160 (47.5)	
N3	2043 (18.8)	2116 (19.5)	
Pathologic M stage, No. (%)			0.910
M1a	2608 (24.0)	2585 (23.8)	
M1b	5125 (47.2)	5154 (47.5)	
M1c	3124 (28.8)	3118 (28.7)	
Involvement of bone, No. (%)			0.834
No	6683 (61.6)	6698 (61.7)	
Yes	4174 (38.4)	4159 (38.3)	
Involvement of brain, No. (%)			0.916
No	7787 (71.7)	7780 (71.7)	
Yes	3070 (28.3)	3077 (28.3)	
Involvement of liver, No. (%)			0.832
No	8907 (82.0)	8919 (82.1)	
Yes	1950 (18.0)	1938 (17.9)	
Involvement of lung, No. (%)			0.771
No	7397 (68.1)	7417 (68.3)	
Yes	3460 (31.9)	3440 (31.7)	

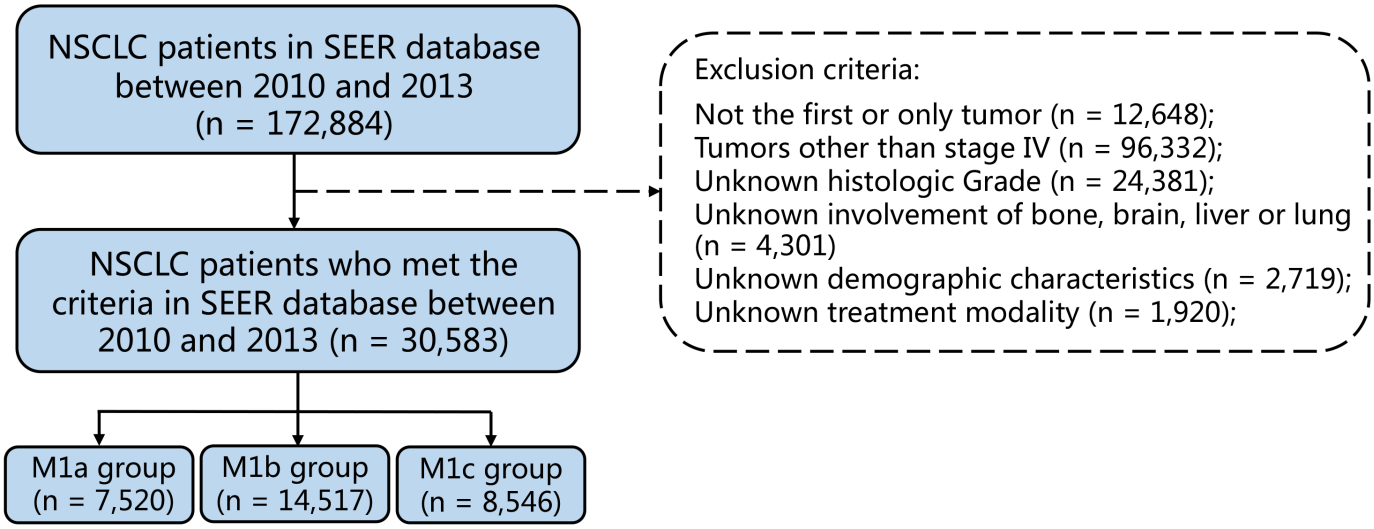

Figure 1. Flow chart of patient screening.

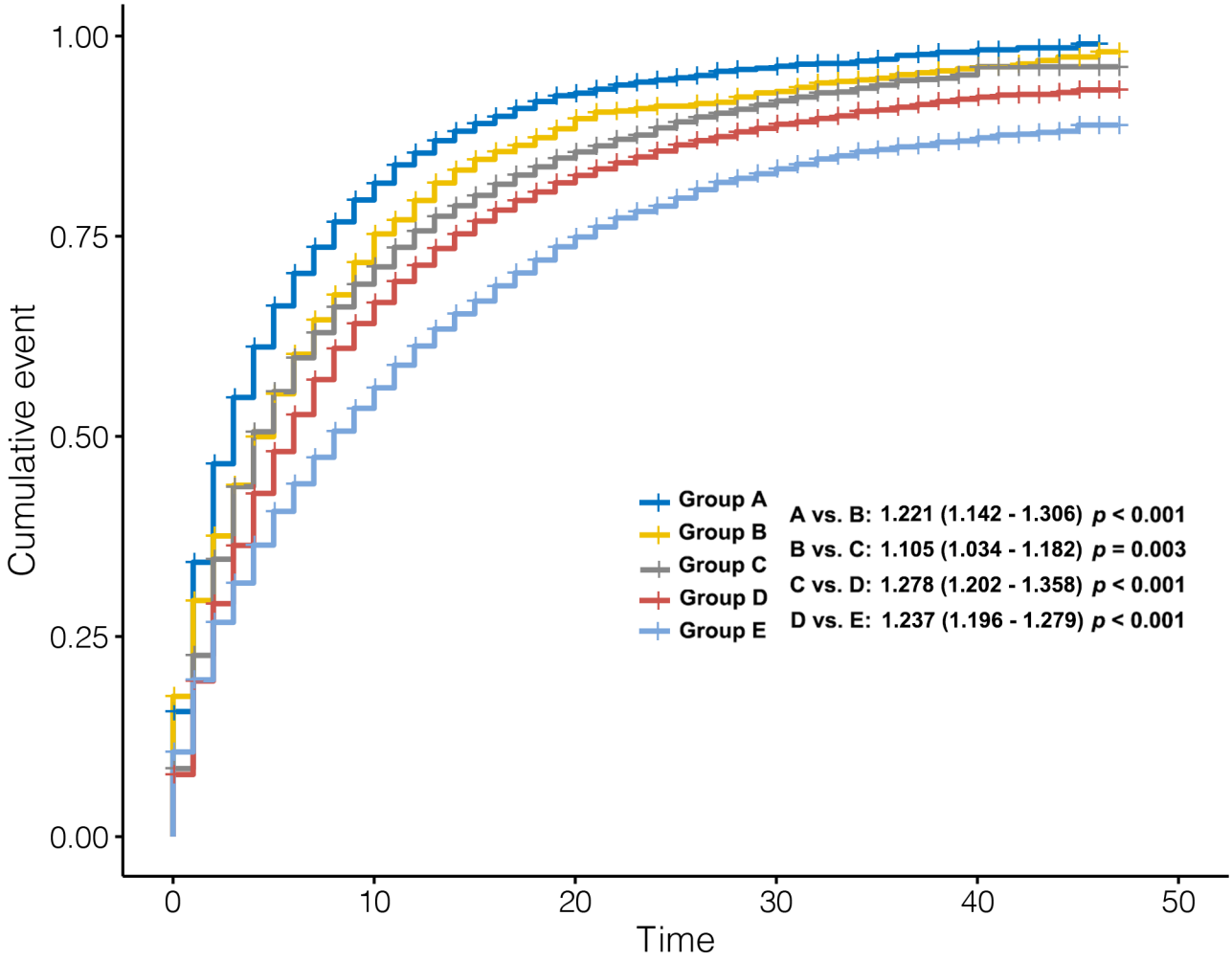

Figure 2. Cumulative incidence curves of cancer–specific mortality for different groups. Patients in group A were diagnosed as M1c NSCLC with involvement of liver; patients in group B were diagnosed as M1c NSCLC without involvement of liver; patients in group C were diagnosed as M1b NSCLC with involvement of liver; patients in group D were diagnosed as M1b NSCLC without involvement of liver; patients in group E were diagnosed as M1a NSCLC.

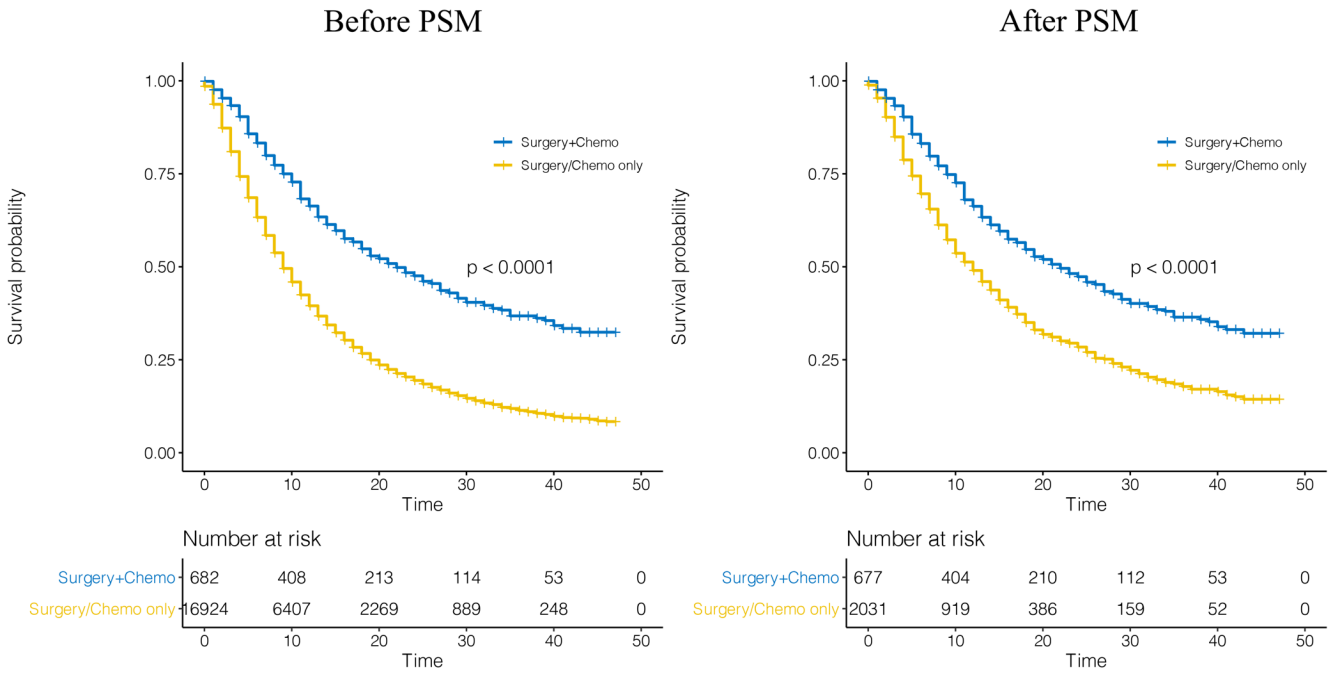

Figure 3. Survival curves of patients receiving surgery plus chemotherapy and chemotherapy or surgery only before and after propensity-score matching (PSM).

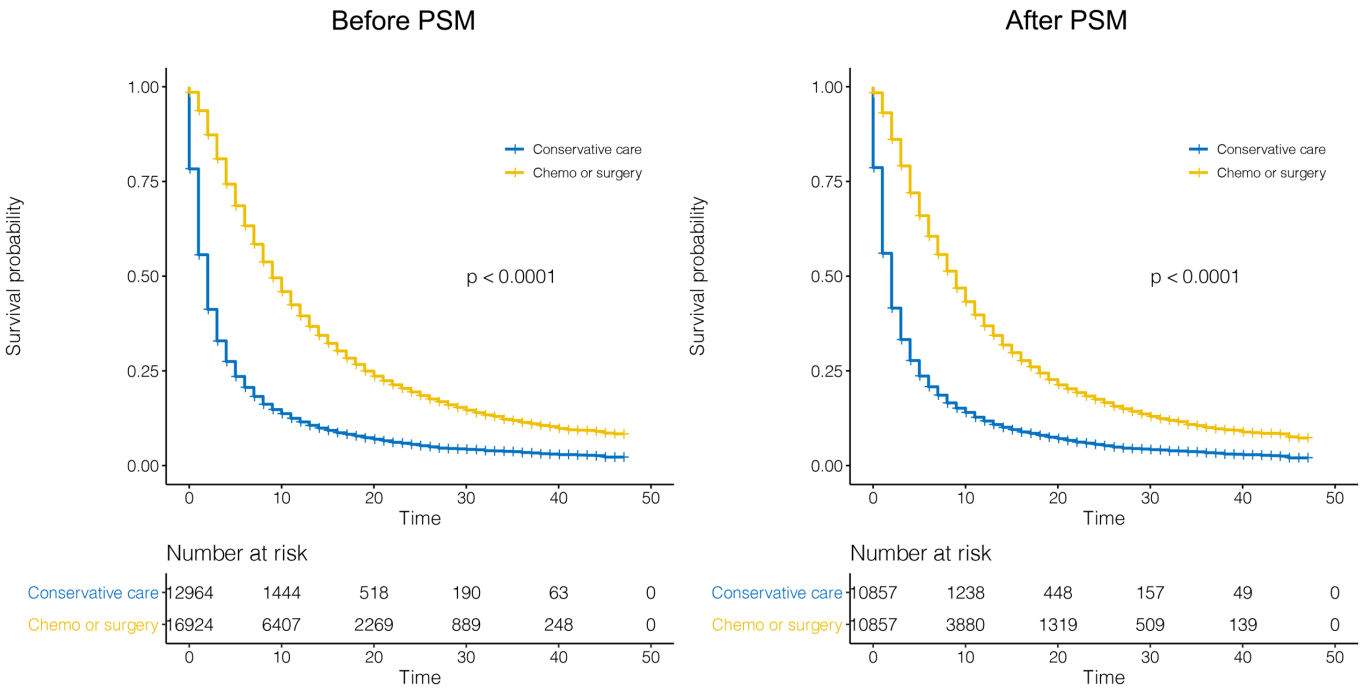

Figure 4. Survival curves of patients receiving no therapy and chemotherapy or surgery only before and after propensity-score matching (PSM).