Peer Review File
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Reviewer A:

I am sincerely grateful for the opportunity to review the original article "Preliminary experience of surgery after neoadjuvant immunotherapy combined with chemotherapy for stage-IIIB non-small cell lung cancer."

The authors' clinical research focuses on neoadjuvant immunotherapy + chemotherapy combined with surgery for stage IIIB non-small cell lung cancer.

As you know, the term neoadjuvant therapy is now used for inoperable patients in a variety of papers. On the other hand, many physicians define neoadjuvant therapy as a treatment for patients who are deemed operable before surgery to reduce the risk of downstaging and micrometastases. Those who use such terminology are: If a patient is considered inoperable at first, for example, after receiving immunotherapy plus chemotherapy or chemoradiotherapy, and then is deemed operable, they call it conversion therapy (surgery) or salvage surgery (the terminology differs depending on the organ). In this group of physicians, neoadjuvant therapy is interpreted as meaning that the patient was operable from the beginning.

Since the present study focused on clinical stage IIIB, I believe it is necessary to firmly indicate whether the patients were judged operable before the immunotherapy and chemotherapy treatment to avoid misinterpretation of the present paper.

The study included 30 patients with stage IIIB non-small cell lung cancer who underwent neoadjuvant immunotherapy plus chemotherapy. Nineteen patients (63%) underwent surgery, and all patients achieved R0 resection. This means that all lymph nodes considered metastatic nodes before the adjuvant treatment were pathologically reviewed, and the dissected margins of the lymph nodes were negative. In fact, did the authors pathologically verify all lymph nodes that were diagnosed as positive prior to treatment?

The results of this study showed that the major pathological response (MPR) rate was 73.7% (14/19), and the pathological complete response rate was 47.4% (9/19). These are excellent results. Unfortunately, two patients developed bronchopleural fistula as a postoperative complication, and one patient died, but overall, the results are amazing.

On the other hand, because of the excellent results of this study, appropriate presentation is

essential. At this time, there are several concerns about this paper, and I would appreciate your addressing or responding to the following questions and, if necessary, modifying the paper as required.

Issues:

#1. Unpacking past reports, an accurate clinical diagnosis of N2 is difficult (and likely the same for N3). A report of a retrospective study of 11,663 resected lung cancer cases showed that 800 cases diagnosed with clinical stage IIIA N2 were pathologically N0: 271 cases, N1: 75 cases, N2: 436 cases, and N3: 18 cases, indicating that 43% were over-diagnosed (1). In a paper such as this clinical study, I believe it is very important to verify pathologically that what is diagnosed as a metastatic lymph node by imaging is a lymph node metastasis using EBUS-TBNA or mediastinoscopy.

My question is, has the N2N3 of the authors and others been pathologically diagnosed by EBUS-TBNA or other methods before neoadjuvant therapy? If not, about 40% of the over-diagnosis may be present if I consider the abovementioned paper (1).

(1) Yoshino I, Yoshida S, Miyaoka E, et al.; Japanese Joint Committee of Lung Cancer Registration. Surgical outcome of stage IIIA- cN2/pN2 non-small-cell lung cancer patients in Japanese lung cancer registry study in 2004. J Thorac Oncol. 2012; 7(5): 850-5.

Answer: Thanks for the advice.

We have added the diagnostic methods of N2N3 in the 30 patients (see line 163-168).

Only 20/30 patients undertook mediastinoscopy surgery or EBUS-TBNA to be diagnosed as N2 or N3, over-diagnosis may be present in the other 10 patients, we added this in the limitations of this study (see line 312-314).

#2. In this paper, only 19 patients were treated with neoadjuvant therapy followed by surgery, which was successful in all cases. Considering the number of patients, it is not impossible to describe all the cases, and I believe each case is an essential piece of data. I want to ask the authors to provide the following information on the 19 patients who underwent surgery: diagnosis and staging before neoadjuvant therapy, whether or not the patient was deemed operable before treatment, details of neoadjuvant therapy and its efficacy, details of the surgery (was the contralateral hilar, mediastinal, or other lymph nodes resected?)), pathology results, and postoperative course.

Answer: Thanks for the advice, we showed the operation details of the 19 patients in the part "***Operation details after treatment***" (see line 190-211) and table 2.

#3. If this paper could present each case in detail as described above, it might be possible to omit Figures 1 and 2.

Answer: Thanks for the advice. Figure 1 illustrates the comparison of the patient's condition before and after treatment and Figure 2 highlights the patients' down staging. So we tend to keep Figure 1 and 2.

#4. The following points should be clearly stated in this paper.
(1) Were the 30 patients in this paper judged to be operable before treatment?
(2) What was the reason they were judged to be inoperable?
(3) It would be helpful to include a description of the indications for surgery for stage IIIB NSCLC at your hospital.
Answer:
(1) The 30 patients in this paper were judged to be operable before treatment, we added the judgment criteria in Inclusion criteria (see line 110-111).
(2) The reason they were judged to be inoperable were listed in Operation details after treatment (see line 191-194).
(3) The description of the indications for surgery for stage IIIB NSCLC at our hospital were listed in Inclusion criteria (see line 110-111).

5. Although this is a double-blind peer review, and I cannot confirm the authors' names, please include the pathologist's name (the person responsible for the pathology diagnosis) as a co-author.
Answer: The pathological results were confirmed by the same pathologist, but he refused to be a co-author.

Reviewer B:

The investigators of "Preliminary experience of surgery after neoadjuvant immunotherapy combined with chemotherapy for stage IIIB non-small cell lung cancer" present their experience with 30 patients, of which 19 underwent resection. As sort of a "pilot" study on the safety and feasibility of this operation, I think their results are worth disseminating as this in an evolving yet timely topic given the recent advent of neoadjuvant chemoimmunotherapy for locally advanced disease. The indications for consideration of patients for surgical therapy for stage IIIB (and multistation IIIA) remains unclear. My comments/questions below:
1. I recommend being more specific about the T and N staging of IIIB patients in the introduction (lines 54-56). This includes patients who are N3 and T3N2 or T4N2.
Answer: Thanks for the advice. We modified the T and N staging of IIIB patients in the introduction (see line 72).

2. I would recommend "enlargement" rather than "aggravation" (line 152).

Answer: Thanks for the advice. We changed “aggravation” into “enlargement”.

3. We need more details about how patients were selected for surgery, and what type of response these patients had had radiographically prior to surgery.
Answer: Thanks for the advice. The 30 patients in this paper were judged to be operable before treatment, we added the judgment criteria in Inclusion criteria (see line 110-111). All the 19 patients who undertook surgery had PR radiographically prior to surgery (see line 198-199).

4. The fact that over 10% of patients developed a postoperative bronchopleural fistula is notable, and justifies additional discussion. This is a serious perioperative complication that is quite rare. We need information about what type of operation these 2 patients received.
Answer: 1 patient undertook three-port thoracoscopic right upper lobectomy and the other one undertook open left upper sleeve lobectomy.

5. We need some definitions for CR, PR, SD, PD, ORR, and DCR.
Answer: The definitions for CR, PR, SD, PD, ORR, and DCR were in part “***Evaluation method***” (see line 132-146).

6. Does MPR including pCR (line 176)?
Answer: Yes, MPR includes pCR.

7. I would recommend using “downstaging” rather than “depression” (lines 177-178).
Answer: Thanks for the advice. We changed “depression” into “downstaging”.

8. Were patients confirmed as being N2 or N3 with tissue biopsy prior to neoadjuvant treatment? Details of how they were staged is necessary, including imaging findings (how many were radiographically N3) and procedures (how many underwent EBUS and mediastinoscopy).
Answer: Thanks for the advice.We have added the diagnostic methods of N2N3 in the 30 patients (see line 163-168). The details of how they were staged were showed in Table1.

9. How were patients in the non-surgical group treated?
Answer: Of the 30 patients, two patients (7%) were lost due to follow up, five patients (17%) showed progression and switched to curative-intent radiotherapy and chemotherapy, three patients (10%) had SD and choose non-surgical treatment, one patient (3%) experienced a decline in lung function after treatment (see line 191-194).

10. Can the investigators provide information about overall survival?

Answer: The time of follow up was too short to provide information about overall survival.

11. It is not clear whether the section on “adverse reactions” refers to reactions to neoadjuvant therapy. If so, I recommend this is located before the section on “operation details after treatment”.
Answer: Thanks for the advice. The “adverse reactions” refers to reactions to neoadjuvant therapy and we located it before the section on “operation details after treatment”.

12. Citations on the historical data for progression free survival (and overall survival, if you have this data for your cohort) for stage IIIB patients should be provided in the discussion section.
Answer: We have provided the historical data for progression free survival in the discussion section (see line 282-286).

13. The main issue overall with this study is that there is likely a large selection bias in favor of improved outcomes for the patients who undergo surgery after neoadjuvant therapy, compared to those who did not. The former group is likely comprised of patients that respond better to therapy (whether they had a better radiologic response and/or fewer adverse reactions), and may be healthier in general. There needs to be a table comparing characteristics of surgical vs non-surgical patients.
Answer: We have mentioned that due to the small sample size, it was not possible to conduct propensity score matching (see line 317-318).

Reviewer C:

The work has important limitations; The authors make several methodological errors, and attempt to draw conclusions from a study that is really a series of cases. It may have descriptive value, but the authors cannot claim that it is an analytical study.
I believe that the article, to be published, should be corrected in depth, based on these premises.

COMMENTS:
• In the Abstract: The Methods section should summarize the variables analyzed and the statistical management. They do not even include the type of study carried out, which is ultimately a more or less extensive series of cases. The authors do not identify their main objective, nor the secondary objectives. In the Conclusions, the need to determine adjuvant management is referred to, which in the article is not part of the objectives.
Answer: The main objective of our study is to examine the outcomes of surgery after

neoadjuvant immunotherapy combined with chemotherapy for stage-IIIB NSCLC. We deleted the need to determine adjuvant management.

• L.56-57: “Stage-IIIB NSCLC belongs to locally advanced lung cancer”; They really are cancers in a LOCOREGIONALLY ADVANCED situation.
Answer: Thanks for the advice. We changed “locally” into “locoregionally”.

• L.90-95: In this numerical list of the inclusion criteria, they are indicated with Roman numerals in parentheses; However, the first indication, (I), does not appear.
Answer: We added the first indication, (I) (see line 110).

• In the inclusion criteria, respiratory/cardiac functional assessment does not appear. They refer to exclusion criteria, but in a very non-specific way. Respiratory function tests are decisive in patients who will later undergo lung resection surgery.
Answer: We added “normal cardiopulmonary function” into the inclusion criteria (see line 115).

• The abbreviation PR, partial response, appears before (L.109) the authors explain its meaning (L.116).
Answer: We added “(partial response)” after PR (see line 129).

• L.104-105: The wide variety of drugs used for immunotherapy is striking; none is nivolumab.
Answer: We didn’t use nivolumab in these 30 patients.

• In Statistical Method he talks about the comparison of variables, in a study that a priori seems descriptive, not analytical; The groups to be compared, if any, are not described.
Answer: The groups to be compared were described in Table 2.

• The criteria defining ORR and DCR are not specified.
Answer: The criteria defining ORR and DCR were described in part “Evaluation method” (see line 132-146).

• It is striking that the evaluation was done every two cycles, and yet, 2 patients received only one cycle.
Answer: These two patent were lost of follow-up after one cycle.

• Table 2, errata: It says "There-ports", it should say "Three-ports".
Answer: Thanks for the advice. We modified “There” into “Three”.

• As a prerequisite for the application of the chi-square test, it must be taken into account that all expected frequencies must be greater than 5. The sample size available to the authors does not allow it to be applied adequately, invalidating the analytical results presented by the authors.
Answer: Prospective randomized controlled studies with larger sample sizes are needed for further validation.

• Follow-up results: A comparison is made between operated and non-operated patients, but we do not know if both groups are really comparable, because no objective of the study establishes a comparison between both possible cohorts.
Answer: Thanks for the advice. We mentioned this in the limitations: due to the small sample size, it was not possible to conduct propensity score matching (see line 317-318).

• L.221: The authors refer to "navulizumab monotherapy"; they probably mean "nivolumab monotherapy". Or it's probably the name of the drug in the authors' native market; In L.224, the drug is repeated.
Answer: Thanks for the advice. We modified “navulizumab” into “nivolumab”.

• L.239-242: Redundant text, with a typo: they indicate that the patients are in stage IIB, when it is stage IIIB.
Answer: Thanks for the advice. We modified “IIB” into “IIIB”.

• L.253-260: Inference with significant selection bias.
Answer: Thanks for the advice. We mentioned this in the limitations.

• L.263-272: Inference with a statistical bias, due to the sample size. The authors could make a descriptive comparison, but statistical significance is distorted by sample size.
Answer: Thanks for the advice. We mentioned this in the limitations.

• The authors recognize these biases among the limitations of the study.
Answer: Thanks for the advice. We mentioned this in the limitations.

• In Conclusions, the authors state: “While the majority of patients in this study were able to undergo surgery, post neoadjuvant pulmonary resection was associated with a relatively high rate of morbidity and mortality”. However, the authors do not analyze it in the discussion, and the results they report do not seem to reveal a worrying series of complications. In the conclusions of the abstract, they emphasize: Neoadjuvant immunotherapy and chemotherapy combined with surgery in patients with stage-IIIB NSCLC is safe and feasible.

Answer: We mentioned in the discussion: The safety of neoadjuvant immunotherapy combined with chemotherapy is also a matter of concern (see line 302-303).

Reviewer D

This study analyzes a population of patients with stage IIIB lung cancer treated with surgery after neoadjuvant immunochemotherapy. This population historically was not eligible for upfront surgery, but with the advent of immunotherapy treatments, new avenues may open for surgical treatment as an option after neoadjuvant therapy. Despite the limited case series, this retrospective study takes an important step in establishing and analyzing data to evaluate whether surgical treatment has an effect on disease-free survival compared to systemic treatment alone.

We have a few minor issues with the paper

1: In the selection of patients, it is not clear, aside from cases of disease progression, what the exclusion criteria for surgery were. Could you clarify them?
Answer: The exclusion criteria for surgery were listed in Operation details after treatment (see line 191-194).

2: Among the patients, did you notice differences in treatment response and/or PFS between those with different PDL-1 scores? Specifically, were there differences in the number of major pathological responses between patients with high and low PDL-1 expression?
Answer: The study was a retrospective study with a small sample size, so it is hard to catch every patient's PDL-1 score. Prospective randomized controlled studies with larger sample sizes are needed for further validation and we should focus on the PDL-1 expression too.

3:One of the concerns regarding the operability of patients undergoing neoadjuvant therapy is the potential increase in surgical complexity. The study compares cohorts of patients who underwent two, three, or four cycles of therapy. Compared to patients who did not undergo neoadjuvant therapy, was there an increase in operative time, blood loss, or the development of postoperative complications?
Answer: Thanks for the advice. In our study, there was no significant difference between operative time, blood loss, or the development of postoperative complications between 2 cycles and 3-4cycles. Patients who did not undergo neoadjuvant therapy should also be included and propensity score matching should be conducted.

4: In line 239, the patients are erroneously defined as stage IIB.

Answer: Thanks for the advice. We modified “IIB” into “IIIB”.

Reviewer E

The authors reported the feasibility and efficacy of chemo-immunotherapy as a neoadjuvant setting in patients with stage IIIB non-small cell lung cancer.

1. The inclusion criteria are unclear even if this study is retrospective.
1) How did the authors diagnose an NSCLC by cytology, not histology?
Answer: Thanks for the advice. We modified “cytological” into “histological”.
2) How did the authors diagnose the stage IIIB disease? For example, the case of Figure 1 looked at Stage IIIA disease. How did the authors confirm stage IIIB disease, especially for nodal metastasis?
Answer: The case of Figure1 was diagnosed as stage T4N2M0, IIIB. We have added the diagnostic methods of N2N3 in the 30 patients (see line 165-168).

3) Please add the reason for T3 or T4 disease.
Answer: T3 or T4 disease with N2 were stage IIIB disease.

4) How did the authors select the patients included in this study? The authors used several anti-PD-1 monoclonal antibodies; however, these drugs were not allowed in a neoadjuvant setting. If the authors used these drugs in a clinical research setting, the authors must mention the details of the specific study.
Answer: We signed an informed consent form with the patients before treated.

2. The authors mentioned that stage IIIB disease has been considered an inoperable disease; however, some reports showed that the multimodal therapy, including surgery, showed efficacy for carefully selected T3N2 or T4N2, stage IIIB disease. Of course, N3 disease is usually considered inoperable, and surgery could only be chosen in a salvage manner.
Answer: The 30 patients in this paper were judged to be operable before treatment, we added the judgment criteria in Inclusion criteria (see line 110-111).

3. The authors used many immune checkpoint inhibitors, including pabolizumab, carrelizumab, tirelizumab, xindilizumab, and treprizumab. Again, these drugs cannot be used in a neoadjuvant setting so far; hence, if the authors used these drugs as a part of clinical research, the authors must mention the details of the specific study. In addition, there was no information on how the authors used these immune checkpoint inhibitors in combination with

chemotherapeutic agents on the patients.
Answer: We signed an informed consent form with the patients before treated.

4. The definition of pCR should be reviewed. It is usually defined as no residual tumor in both primary and metastatic lymph nodes, different from the definition of MPR.
Answer: We defined pCR in the part of "***Evaluation method***" (see line 132-146).

5. Nothing was mentioned about the approval of the review ethical board for this study.
Answer: Thanks for the advice. We added it in the part of Methods (see line 101).

6. However, there were only 4 PD cases; why did 11 out of 30 cases not receive surgery in this study, even for these patients who received "neoadjuvant" therapy? How did the authors judge the resectability when the patients enrolled for neoadjuvant treatment?
Answer: The reason they were judged to be inoperable were listed in Operation details after treatment (see line 190-194). The description of the indications for surgery for stage IIIB NSCLC at our hospital were listed in Inclusion criteria (see line 110-111).

7. the survival analysis of this study is meaningless because the treatment protocol was not unified, unfortunately. I am afraid that it may mislead the readers.
Answer: Thanks for the advice. We mentioned in the limitations: Prospective randomized controlled studies with larger sample sizes are needed for further validation.

8. Again, there was no detailed information about each regimen and treated patients. Even for the small number of patients for each treatment, we cannot evaluate the results of this study because it contained different therapies.
Answer: Thanks for the advice. We mentioned in the limitations: Prospective randomized controlled studies with larger sample sizes are needed for further validation.

Reviewer F

Although this study conclusion is plausible, it is poorly supported by the study data.
First of all, only 19 patients underwent surgery, obviously limiting the generalizability of the result. For example, it would be interesting to compare the results obtained with a minimally invasive surgical approach with those obtained with an open approach, but the small sample size does not allow such evaluations. It is also strange that only 63% (19/30) of patients underwent surgery when the objective response rate (ORR) and disease control rate (DCR) of the patients after neoadjuvant therapy evaluated by imaging studies were 70% and 86.7%, respectively. How can you explain this?

Answer: Thanks for the advice. We mentioned in the limitations: Prospective randomized controlled studies with larger sample sizes are needed for further validation.The reason of the 11 patients judged to be inoperable were listed in Operation details after treatment (see line 190-194).

Second, there is a total lack of description of how the lymph node staging was done. There is no mention of PET and EBUS or mediastinoscopy in the manuscript. If you want to evaluate the results and applicability of a complex therapeutic strategy in a specific stage of the disease which is strongly dependent on the infiltration of the mediastinal lymph nodes, these data cannot be missing, knowing how the staging of the mediastinal lymph nodes is fallacious if carried out with the CT scan alone. Please add description of how mediastinal staging was performed.
Answer: Thanks for the advice. We have added the diagnostic methods of N2N3 in the 30 patients (see line 165-168).

Third, there are no data on molecular analysis or expression of PDL-1 in neoplastic cells, which could increase the value of the study. Do you have this data?
Answer: The study was a retrospective study with a small sample size, so it is hard to catch every patient's PDL-1 score. Prospective randomized controlled studies with larger sample sizes are needed for further validation and we should focus on the PDL-1 expression too.

Reviewer G

Authors submitted their manuscript entitled « Preliminary experience of surgery after neoadjuvant immunotherapy combined with chemotherapy for stage-IIIB non-small cell lung cancer" to JTD.
They performed a retrospective study including 30 patients with stage IIIB lung cancer treated with neoadjuvant immunotherapy and chemotherapy. Among them, 19 underwent surgical resection after neoadjuvant therapy.
My comments are below:
1. English is ok.
Answer: Thanks for your affirmation.

2. T3N2M0 tumor is also part of the stage IIIB according to the 8th TNM classification. Sentence line 55 suggests that only T4N2 tumor is involved. According to table 1, 9 patients were deemed T3N2. Please clarify.
Answer: Thanks for the advice. We modified the T and N staging of IIIB patients in the introduction (see line 72).

3. Please precise preoperative staging.

3a. Among N2 patients, please precise how many patient were single-station N2, multi-station N2 or skip N2.

Answer: We mentioned this in the part of ***Postoperative pathological evaluation*** (see line 221-226).

3b. Please also precise if N2 disease was confirmed pathologically (EBUS, EUS, mediastinoscopy) or if N2 status was based on PET-CT.

Answer: Thanks for the advice. We have added the diagnostic methods of N2N3 in the 30 patients (see line 165-168).

3c. Please also defined the type of T3 and T4 tumors (tumor size, multiple tumors, adjacent organ involvement).

Answer: All the T stage were diagnosed by the tumor size (see line 165).

4. Methodology is biased because of the retrospective design, exposing to the risk of selection bias. These patients probably were highly selected to undergo a neoadjuvant therapy and surgery, based on patient fitness and potentially resectable disease (non-bulky nodal disease, T4 because of tumor size rather than adjacent organ invasion). This may explain the high rate of MPR and pCR, through a "selection of winner" effect. This is a serious limitation.

Answer: Thanks for the advice. We mentioned in the limitations: Prospective randomized controlled studies with larger sample sizes are needed for further validation.

5. 19 out of 30 patients were eligible for surgery, which means 11 patients (36.7%) could not proceed with surgery. What treatment did these patient received? Were they able to receive radiotherapy or any local treatment? Or were they all treated with chemotherapy, targeted therapy, or immunotherapy?

Answer: Of the 30 patients, two patients (7%) were lost due to follow up, five patients (17%) showed progression and switched to curative-intent radiotherapy and chemotherapy, three patients (10%) had SD and choose non-surgical treatment, one patient (3%) experienced a decline in lung function after treatment (see line 191-194).

6. The 11/30 (36.7%) non-operated patient showed a median PFS of 14 months, which is shorter compared to the median PFS in the PACIFIC trial. Would authors still suggest neoadjuvant immunotherapy and chemotherapy in potentially favourable stage IIIB, considering that 36.7% of patient won't undergo surgery and have worse survival than in the PACIFIC trial treatment modality?

Answer: As we mentioned in limitations, this study was a retrospective study with a small sample size, so the statistical results might have deviations and/or confounding variables.

Prospective randomized controlled studies with larger sample sizes are needed for further validation.

7. Study is lacking data on surgery quality metrics. Number of lymph node, number of stations evaluated. These parameter are of interest, as they seem to be impacted by neoadjuvant treatment, compared to patient naïve from neoadjuvant treatment. Please consider adding data.
Answer: Thanks for the advice. Patients who did not undergo neoadjuvant therapy should also be included and propensity score matching should be conducted.