Peer Review File

Article Information: Available at http://dx.doi.org/10.21037/tlcr-20-1122

Reviewer A:

Comment 1: The text is largely written in the past tense. This is confusing when, for example, lines 272 to 275 deal with current clinical practice.

Reply 1: we accept this suggestion. For describing this study, the past tense was used. For discussing the current clinical practice, the present tense was used in the revised manuscript.

Changes in the text: we use the present tense to discuss the current clinical practice in the revised manuscript (*Line 278-281; Line 336-339*).

Comment 2: Was a systematic lymph node dissection or lymph node sampling performed during lobectomy? If so, how did these procedures turn out?

Reply 2: This is a very good question. We did not discuss lymph node dissection in this manuscript because this study was not designed to deal with this issue. We routinely performed systemic mediastinal and hilar lymph node dissection for lung invasive adenocarcinoma confirmed by intraoperative frozen section in the past ten years. We did not performed the lymph node dissection for AIS and MIA. Recently, we

find that the prevalence of lymph node metastasis of subsolid lung cancer is very low. According to our previous study, there is no lymph node metastasis for pure GGNs, and 1.4% for part-solid tumors[1,2]. Now we perform selective mediastinal lymphadenectomy for part-solid tumors and pure GGNs larger than 2cm. For pure GGNs less than 2cm, we do not dissect the mediastinal lymph nodes.

Changes in the text: No changes was made in the revised manuscript. (we did not discuss lymph node dissection in this manuscript because this study was not designed to deal with this issue.)

Comment 3: Was an anatomical resection performed for all invasive adenocarcinomas or what was the oncological protocol? This is not evident to me from the table because over 216 patients received only a wedge resection.

Reply 3: According to previous studies, wedge resection or segmentectomy is enough for AIS/MIA, while lobectomy is still indicated for invasive adenocarcinoma[3,4]. Therefore, we routinely choose sublobar resection for AIS/MIA and lobectomy for invasive adenocarcinoma according to intraoperative frozen pathology in our clinical practice[5]. For radiologically GGO predominant invasive adenocarcinoma ≤2cm, we

now prefer to perform segmentectomy based on our previous studies[1,2]. For AIS/MIA, we usually performed wedge resection for peripheral nodules and segmentectomy for deeply located nodules ensuring the safe margin.

Changes in the text: We added the detailed resection protocol in the revised manuscript.(*Line 219-222*).

Comment 4: How were the patients staged preoperatively? How many cases with PET-positive mediastinal lymph nodes were there and were the lymph nodes assessed? The conclusion seems too general if there was no preoperative staging and the lymph node status was unknown. Lymph node metastases may be present, especially in the case of adenocarcinomas. Preoperative rigid bronchoscopy, for example with EBUS technique, can help to clarify lymph node abnormalities. These points should be discussed and the conclusion should be formulated more cautiously.

Reply 4: this is a very good question. In China, PET/CT scan is not routinely applied for preoperative staging because PET/CT scan is not covered by medical insurance. In addition, based on our previous studies, there is no lymph node metastasis for pure GGNs, and only 1.4% for part-solid tumors[1,2]. Therefore, we currently use the high-

resolution CT scan for preoperative N staging for patients with subsolid lung cancer. In this study, there was no patients with clinical N1/2 diseases, and there were only 6 patients (0.98%) with postoperatively pathological N1/2 diseases. We added more details for preoperative staging in the revised manuscript. (*Line 201 & 256*)

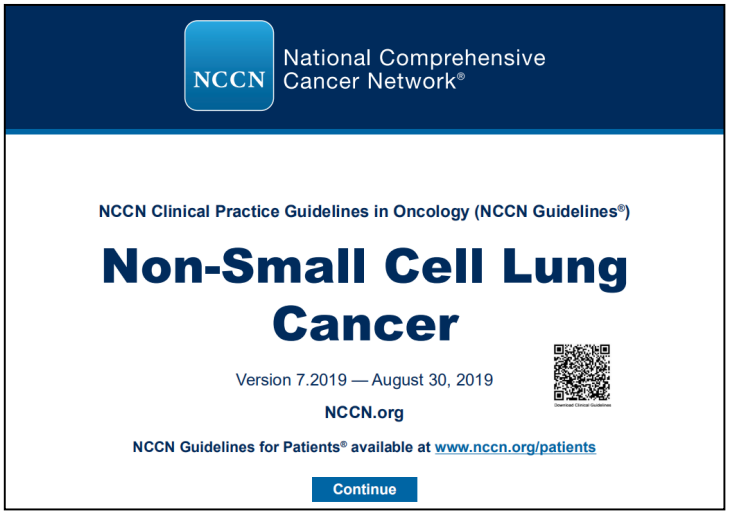
Changes in the text: we added “PET/CT scan was optional for patients with subsolid nodules in this study. ” (*Line 201*) and “There was no N1/2 diseases assessed by HRCT in this study.” (*Line 256*) in the revised manuscript.

Comment 5: The authors state that the rationale for this study is the NCCN guideline, which differs from other guidelines, that bronchoscopy should be performed prior to surgery. First, I have a problem finding the cited study "5. Ettinger DS, Wood DE, Aggarwal C, et al. NCCN Guidelines: Non-Small Cell Lung Cancer, Version 7. 2019 J Natl Compr Canc Netw. 2019 Aug 30". Are the bibliographic data correct? or is meant here: "NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020"? In addition, it should be specified at which point in the guideline a preoperative bronchoscopy is recommended.

Reply 5: we are sorry for this. We can not find “the version 7 of NCCN guidelines”on

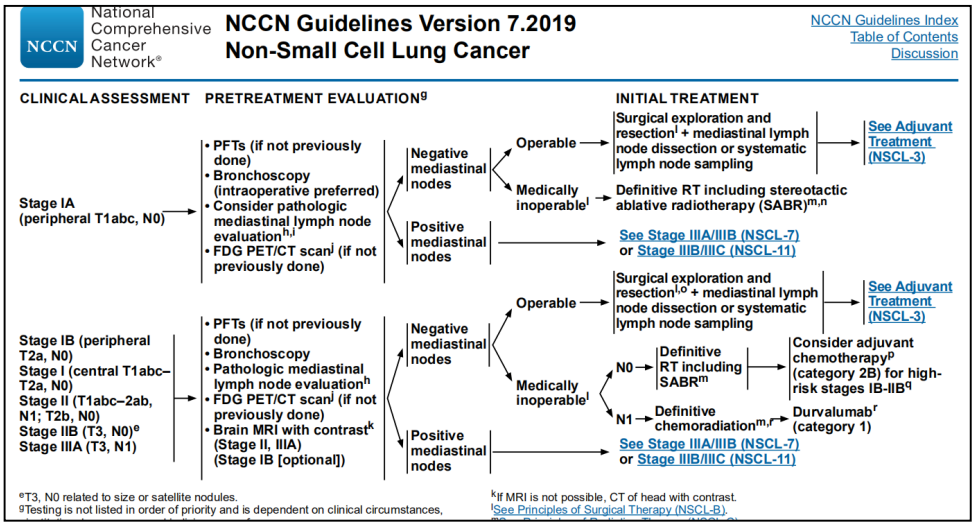
the PubMed. gov, either. However, we can download the guideline from the official website of NCCN. We attached the cover of the guideline as followed. (see Figure 1)

Figure 1:



In this guideline, for stage IA NSCLC, bronchoscopy is recommended for pretreatment evaluation. (see Figure 2)

Figure 2:



Changes in the text: No changes was made in the revised manuscript for this issue.

Comment 6: Line 279: "For patients in western countries, FB examination could be even omitted in the operation room, and this could save the time of the operation". This point has to be discussed in a more precise way, because intraoperative bronchoscopy offers advantages such as position control of the double lumen tubes, especially for anaesthetists who are not experienced in single lung ventilation, suction of secretions before ventilation of the lung and final evaluation of the bronchial stump.These points are not mentioned in the paper. In my opinion, intraoperative bronchoscopy can be used to optimize the intraoperative workflow, which is why bronchoscopy should be used generously during thoracic surgery. The above mentioned sentence of the authors could have the consequence that the availability of an intraoperative bronchoscopy would no longer have to be ensured by default because, according to the authors, it is superfluous.

Reply 6: we accept this comment that intraoperative bronchoscopy offers a lot of advantages not only for anesthesiologists but also for thoracic surgeons, especially when we perform segmentectomy, and especially for anaesthetists who are not experienced in single lung ventilation. Precisely, our meaning is that the procedure of intraoperative bronchoscopy could be simplified according to the results in this study. For example, the deepest area to the carina might be enough for intraoperative bronchoscopy. Sometimes, intraoperative bronchoscopy is more difficult than routine bronchoscopy when patients are in the lateral position.

Changes in the text: we revised the first paragraph in the Discussion section in the manuscript: “Intraoperative bronchoscopy offers several advantages such as position control of the double lumen tubes, especially for anaesthetists who are not experienced in single lung ventilation, suction of secretions before ventilation of the lung and final evaluation of the bronchial stump after the surgery. However, for patients in western countries, FB examination could be simplified in the operation room, and this would save the time of the operation, according to the findings in this study. And for Chinese

patients, it could reduce the latency time for the surgery, and save the average medical expense of about 144 dollar per person." (*Line 283-289*)

Comment 7: the discussion is too short, not one (!) literature passage is cited in the entire discussion. The basic goal of the discussion, namely the evaluation of one's own results taking into account the published literature, is thus not achieved.

Reply 7: we agree that discussion part in the manuscript is short. Because this trial was not complex and the results were simple and concise. We accept this comment and discuss some published studies in the discussion section in the revised manuscript. (*Line 292-319*)

Changes in the text: we have added several references and discussed some published studies in the revised manuscript. (*Line 292-319*)

Comment 8: I would be interested to know who was responsible for bronchoscopy at the study centers in question? From the affiliations of the co-authors it is not always clear in which field you work, for example, whether pneumologists were involved in the work.

Reply 8: this is a very good question. Because our institution is a cancer center, we do not have pneumologists. As a result, we thoracic surgeons perform the bronchoscopy examination for patients in the clinical practice. However, in some branch centers in this trial, such as “Shanghai Zhongshan Hospital” and “Affiliated Hospital of Jiangnan University”, it is the pneumologist who performs the bronchoscopy examination for patients before surgery.

Changes in the text: No changes was made in the revised manuscript for this question.

Comment 9: Does "smoker" only mean "active smoker" and "non-smoker" only "never-smoker" and how were "former smokers" classified?

Reply 9: This is a good question. According to the definition of “smoker” of WHO, smoker means person who smokes more than six months, and non-smoker means person who never smokes. It is unclear how to classify the “former smokers”. According to the inclusion criteria in “The National Lung Screening Trial, NLST”, people who quit smoking less than 15 years were included[6]. It is necessary to set the cut-off value of smoking cessation years for former smokers, but currently it is unclear.

In this study, smoker means active smoker, and non-smoker means never-smoker. Heavy smokers (smoking index ≥400/year) were excluded in this study.

Changes in the text: No changes was made in the revised manuscript for this point.

Comment 10: Was the subtype of Invasive Adenocarcinomas indicated by the pathology? If so, how did they turn out proportionately?

Reply 10: there were 343 invasive adenocarcinomas (IADs) pathologically confirmed in this study. Most of them had mixed subtypes. The percentage of acinar predominant IADs was 60.4% (207/343), percentage of papillary predominant IADs was 18.4% (63/343), percentage of lepidic predominant IADs was 19.5% (67/343), percentage of mucinous adenocarcinomas was 1.4% (5/343), percentage of solid predominant IADs was 0.3% (1/343), and there was no micropapillary predominant IAD in this study. We did not mention the subtypes of IADs in this manuscript because this study did not aim to address this issue.

Changes in the text: No changes was made in the revised manuscript for this question.

Reviewer B:

Comment 1: The difference and originality between the authors article and the previous articles (the references below) should be clarify in discussion

-Current reference 2) Schwarz C, et al. Value of flexible bronchoscopy in the 383 pre-operative work-up of solitary pulmonary nodules. Eur Respir J 2013; 41: 384 177-82.

-Current reference 6) Zhang Y, et al. Is bronchoscopy necessary in the preoperative 395 workup of a solitary pulmonary nodule? J Thorac Cardiovasc Surg 2019; 150(1): 396 36-40.

-Reference) Jo KW, et al. Value of flexible bronchoscopy for the preoperative assessment of NSCLC diagnosed using percutaneous core needle biopsy. Thorac Cardiovasc Surg 2014 ;62(7):593-8.

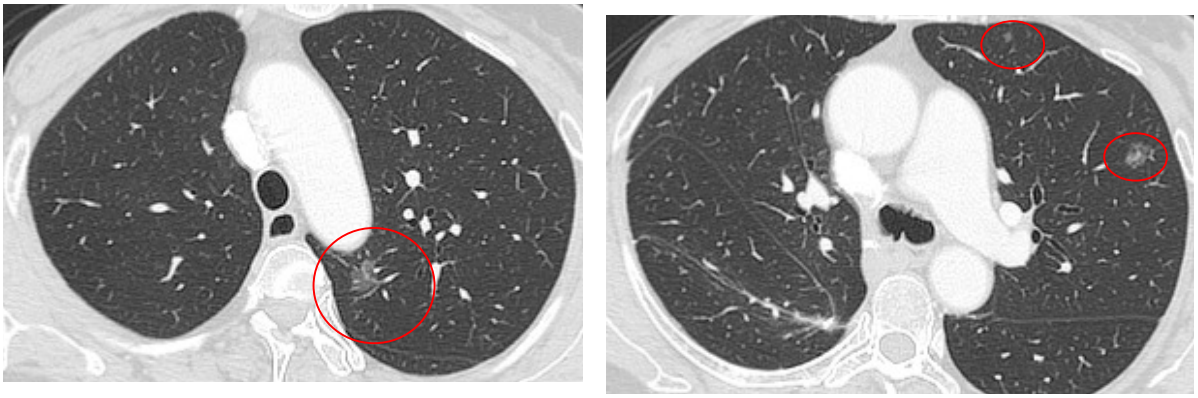
Reply 1: This is a very good suggestion. We have discussed these studies in the Discussion section in the revised manuscript.

Changes in the text: We have discussed these studies in the revised manuscript. (*Line 292-319*)

Comment 2: It is better to show representative CT figures of subsolid (expecially, multifocal nodules). Separate tumor nodules in the same lobe is cT3.

Reply 2: This is a very good suggestion. We have added the representative CT figure of subsolid nodules in the revised manuscript.(*Line 198*) According to our previous studies, separate subsolid nodules in the same lobe should be regarded as multiple primary malignancies[7,8]. For example, this patient had three simultaneous subsolid nodules on left upper lobe. (see Figure 3) She received VATS sublobar resection for the three nodules, and the final pathology indicated all of them were minimal invasive adenocarcinomas.

Figure 3:



Changes in the text: We have added the representative CT figure of subsolid nodules in the revised manuscript. (*Line 198*)

Comment 3: Please described the results of the FB procedures using a brush, needle, forceps or cytologic washing. Were any patients diagnosed with benign diseases on the procedures? In this sense, it is necessary to refer to the following reference article and describe the difference from previous articles.-Reference) Lim JH. et al. The optimal sequence of bronchial brushing and washing for diagnosing peripheral lung cancer using non-guided flexible bronchoscopy. Sci Rep 2020;10:1036.

Reply 3: This is a good question. In this study, there was one adenocarcinoma confirmed by the FB procedure using forceps. No benign disease was diagnosed by these FB procedures. We have discussed this point in the discussion section in the revised manuscript. (*Line 312-316*)

Changes in the text:we have discussed this point in the revised manuscript. (*Line 312-316*)

Comment 4: What is the final diagnosis of stage 0 (n=23)?

Reply 4: the final diagnosis of stage 0 was Adenocarcinoma in situ (AIS). According to the TNM staging of IASLC (Edition 8), AIS is classified as stage 0.

Changes in the text: No changes was made in the revised manuscript for this point.

Comment 5: What kind of tests were performed to determine the staging of lung cancer? PET FDG and/or Brain MRI and/or bone scan??? Were the tests performed before or after surgery?

Reply 5: this is a very good question. In China, PET/CT scan is not routinely applied for preoperative staging because it is not covered by medical insurance. Generally, brain MRI, bone scan and cervical and abdominal ultrasonography are applied for preoperative staging for lung cancer patients in our clinical practice. However, brain MRI is not mandatory for clinical stage I patients in our clinical practice, because brain MRI is not routinely recommended for them by NCCN guideline. And according to our recent study, bone scan is not necessary for patients with subsolid lung cancer[9]. So now bone scan is not applied for patients with subsolid lung cancer. Therefore, we currently use the high-resolution CT scan and cervical and abdominal ultrasonography for patients with subsolid lung cancer for preoperative staging. In this trial, high-resolution CT scan, bone scan and cervical and abdominal ultrasonography were applied for preoperative staging. We added more details for preoperative staging in the revised manuscript. (*Line 201*)

Changes in the text: we added “PET/CT scan was optional for patients with subsolid nodules in this study” (*Line 201*)