Peer Review File

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COMMENT 1: The author concluded "a negative result by endosonographic restaging requires confirmation by a surgical procedure." In the main document, the author described some limitations on re-mediastinoscopy including technical difficulty, relatively high morbidity and mortality, and low sensitivity. In addition, the accuracy of re-mediastinoscopy seems to be comparable to endosonography. Why does the author recommend re-mediastinoscopy for patients with negative endosonographic results?

REPLY 1:

• The pooled sensitivity and negative predictive value of endosonography are not satisfactorily high to rely on and there is about 20-25% false-negative rate. Many large studies, several meta-analyses and two guidelines recommend surgical procedures (mediastinoscopy/VATS) for confirming the stage in these false-negative cases as also recommended in staging. So, the author has given the evidence-based recommendations from the current literature and not just her own ideas and recommendations in this article which is a review and not a study.

• Please note that in Figure 1 there are two options shown for the cases with negative endosonographic results:

(1) VATS or thoracotomy for treatment or

(2) Mediastinoscopy or VATS for restaging

The final decision should be made by the multidisciplinary team for a tailored management of the particular case.

• Furthermore, there are limitations in the current literature on restaging and thus, the current evidence is as much as that mentioned in the article.

Please see the revised parts in the text, table and figure:

(1) The parts that have already emphasized clearly what is explained in my reply above.

(2) The sentence below added on page 14:

"*A clinically reasonable pathway for mediastinal restaging should be implemented and tailored for each individual patient through a discussion in a multidisciplinary team consisting pulmonologists, thoracic surgeons, medical oncologists and radiation oncologists (28,29,70) (Figure 1).*"

COMMENT 2: It is expected that there were inevitable limitations due to the design (literature review) of the article, but is it possible to check the time interval from the last neoadjuvant treatment to restaging procedure? The time interval from neoadjuvant treatment to restaging seems to be important in judging whether there is a residual tumor.

REPLY 2:

• The pertinent literature on the time interval from the completion of neoadjuvant treatment to restaging procedure has been searched thoroughly. There is no strong evidence or consensus on this issue. There is only one retrospective study (newly added reference 57) assessing the optimal time to restaging by PET/CT. In this study, the optimal interval was found to be about 1 month but varying intervals (2 weeks-12 weeks) have been used in different studies.

• The phrase below with related references are added to the text on page 11:

"*In the studies used for the pooled data analyses most important limitations are lack of standardization in diagnostic testing and treatment: variations in the time interval between the completion of neoadjuvant therapy and restaging by CT, PET/CT, endosonography or surgical procedures [optimally about 1 month (57) but varying from 2 to 12 weeks (8,27,57,58)]…*"

• The numbers of the references after the addition of new reference 57 have been revised in the text, references and figure as required.

COMMENT 3: In Table 1, how can you explain the low sensitivity of VATS? Could it be understood that it was because the contralateral LN could not be identified by VATS?

REPLY 3:

• As a reply to this question, the sentences given below are added to the text on pages 4-5.

"*Restaging by VATS, although feasible, is limited to one hemithorax because it requires single-lung ventilation. The sensitivity, specificity and negative predictive value of VATS for restaging after induction therapy were reported to be 67%, 100 and 73%, respectively by only one prospective multi-institutional trial. VATS restaged the mediastinum in 69% of patients but failed in 31% owing to the unmet pre-study feasibility endpoints in 38%, false-negative stations in 15%, necessity to abort the procedure due to pleural adhesions, tumor bulk, airway injury and inability to achieve atelectasis in 16% (15).*"

• The reference numbers are revised in the text, table and figure as required after the addition of new reference 15.

COMMENT 4: In Line 262, in the description related to the needle size; In theory, larger (19-G) and smaller needles (25-G) are expected to obtain more diagnostic and/or adequate histologic and cytologic samples, respectively, what is the reason that a smaller needle (25G) can obtain a better quality cytologic sample? I think a larger needle would be more effective at getting high quality samples.

REPLY 4:

• As a reply to this question, the sentence below is added with 3 new references on page 13:

"*In theory, larger (19-gauge) needles are expected to obtain more diagnostic and adequate histologic and cytologic samples than smaller needles. However, in real-world practice larger needles have not provided significantly higher but rather comparable diagnostic performance in EBUS-TBNA whether it is 21-gauge versus 22-gauge (64,65), 22-gauge versus 25-gauge (66), or 19-gauge versus 21- or 22-gauge (67,68). More frequently obtained bloody cytologic specimens and inadequate specimens due to more difficulty in puncturing the tissue with a 19-gauge needle might have caused its lower than expected performance (68).*"

• The reference numbers are revised again in the text, table and figure after the addition of new references 66, 67, 68.