TLCR TRANSLATIONAL LUNG CANCER RESEARCH
AN OPEN ACCESS JOURNAL FOCUSING ON CLOSING THE GAP BETWEEN "BENCH AND BEDSIDE"
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Peer Review File

Article Information: https://dx.doi.org/10.21037/tlcr-21-364

Reviewer A

Comment 1: Very nice study, there are some minor typos. I recommend proofreading by a native speaker.
Reply 1: Thank you for your kind words of appreciation. Our paper had been proofread by a native speaker before submission (as appreciated in the Acknowledgements section). We will once more review our paper on typos and address them accordingly.
Changes in the text: See changes throughout the manuscript. See page 6 line 100, page 7 line 127, page 8 line 133, page 10 line 185, page 13 line 244, page 18 line 359.

Reviewer B

Comment 1: This study compared the surgical outcomes of VAMLA and VAM. By the way, I wasn't very interested in the comparison between VAMLA and VAM in your study. It is a natural result that VAMLA is more accurate in lymph node staging than VAM. Moreover, it is difficult to compare VAMs conducted in the past (2007-2011) with VAMLAs conducted recently (2011-2018). This is because the gap between 2007 and 2018 is so large that not only surgical techniques but also other environmental influences will be significant. And the statistical comparison between the VAM group and the VAMLA group is not organized, so the results of the statistics are not accurately conveyed. Comparisons between the two heterogeneous groups are meaningless. For this study to be meaningful, it must be a randomized controlled trail of VAMLA and VAM conducted in the same environment by the same surgeons.
Reply 1: Thank you for your critical evaluation of our submission. We understand your criticism that our current study goes hand in hand with significant drawbacks due to its retrospective study design and the enrollment period used. Ideally, we would have performed a randomized controlled trial with adequate power. In the absence of randomized trails addressing this subject, cohort studies should be regarded as a step up to randomized trials. Such studies may also provide evidence, however, should carefully be interpreted in the light of their inherent domains of bias (which should be adequately addressed for the sake of clarity and transparency, as has been done in the presented manuscript).
Our study does provide insights into the improved staging results obtained using VAMLA in comparison with VAM in a single institution high-volume peripheral expertise center, while giving us a real-life impression of the complications associated with this procedure.
Nevertheless, since we fully agree with your comment, the limitations section has been amended and future directions have been provided while the conclusion has been amended as well.
Changes in text: see changes on page 20 line 410-412 and page 22 line 459-460.

Reviewer C

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The Authors addressed one of the most important issues in contemporary thoracic surgery, i.e., mediastinal staging of lung cancer. The paper is well-written, and it provides interesting data. I do not have major reservation regarding its structure, clarity and the results provided.
My remarks are of general nature and, in fact, the Authors addressed most of them in the 'Discussion' section.
Below there are some comments, which the Authors may find useful while preparing the final version of the article.

Comment 1: Initial diagnostic work-up included 'EBUS and/or EUS'. Although not stated directly, I assume that combined EBUS and EUS, referred to as Combined Ultrasound (CUS), was not used in patients included in this study. As there is convincing evidence that CUS performs better than either EBUS or EUS alone, the question may be asked if VAM or VAMLA would have improve preoperative staging if CUS had been routinely performed.
In other words, the present study analyses additional value of surgical staging following negative, but suboptimal, minimally-invasive assessment.
Reply 1: Thank you for your valuable comment. CUS was not instituted consistently throughout the work-up, implantation of such can further improve the diagnostic strategy, thereby reducing the number of patients requiring a VAM(LA)-procedure. In order to assess the diagnostic yield in the pre-operative phase, in a subsequent study protocol we will compare EBUS, EUS and CUS. Furthermore, in the 'future perspectives' section of our manuscript we elaborate on the MEDIASTrial, investigating whether dual endosonography alone is non-inferior to the addition of subsequent surgical mediastinoscopy.
Changes in text: Added a reference to the ESGE/ERS/ESTS in the future perspective section. See page 20 line 416-418.

Comment 2: According to the ESTS guidelines, surgical staging may be omitted in centres with the rate of N2 undetected by EBUS/EUS being <10%. It seems that strategy aimed at increasing the diagnostic yield of the preoperative minimally-invasive staging (imaging followed by CUS) is more consistent with the general philosophy of 'minimally invasive mediastinal staging and maximally extensive intraoperative lymph node dissection'.
Reply 2: We totally agree with this statement. At current we are preparing a retrospective analysis of our minimally invasive staging procedures prior to surgical mediastinal staging (EBUS, EUS, CUS) to further improve our diagnostic strategy.
Changes in text: no changes were made.

Comment 3: Lung resection was performed 1 week after VAM/VAMLA, with all consequences of dissection in a distorted anatomy. Although there is no evidence of increased risk of complications of lung resection in such situation, repeated dissection of mediastinal and hilar structures is technically more demanding. It would be good to know if the Authors found any difference in complications and postoperative course in this study.
Reply 3: During subsequent lung resection, additional lymph node dissection is performed to comply to European guidelines. We agree that anatomical resection following VAM(LA) may be technically more demanding given the present tissue reaction/mediastinal induration. In our experience, the mediastinal tissue reaction is absent to minor in the first week after VAMLA,

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but increases in postoperative week two and three. Therefore, lung resections were typically planned five to seven days after VAM/VAMLA. Moreover, stations that were already resected in toto during VAMLA, were not re-explored. Depending on tumor location, lymph node stations other than 2, 4 and 7 were thus dissected during anatomic resection (i.e., stations 5, 6, 8 and 9 where applicable). These stations are in previously untouched areas and are thus unlikely to trouble resection. In contrast, VAM requires re-evaluation of stations 2, 4 and 7, potentially troubling the ease of anatomical resection.

Unfortunately, we have not acquired data on the complications after anatomical resection. However, evaluating the difference regarding complications after anatomical resection may be of great interest for future research given the preceding differences between anatomical resection after respectively VAM and VAMLA. The discussion section was amended accordingly.

Changes in text: adjustments in work-up and surgical techniques were made to clarify mediastinal resection during subsequent anatomical resection. In addition, the discussion section was amended. See changes on page 8 line 146-158 and page 16 line 320-329.

Comment 4: As the Authors mention, 'missed mediastinal metastases were single station in all but one patient'. For minimal N2 disease, there is no evidence showing superiority of pre- versus postoperative chemotherapy. This rises a question, whether additional surgical procedure (VAM or VAMLA) is justified. Moreover, if routine CUS had been used preoperatively, the risk of missing a 'more-than-minimal' N2 would be probably even lower.

This question is particularly relevant in the light of the complications associated with VAM/VAMLA and the 10-15% rate of patients, in whom general condition deteriorated following surgical staging, making them inoperable.

Reply 4: Thank you for this important comment. In the VAMLA and VAM group, respectively 5% and 10% of patients without N2 disease found after surgical mediastinal staging did not undergo subsequent anatomical lung resection. This resulted from the primary objective for mediastinal staging being assessment of nodal status to determine chemoradiation treatment strategy in these selected patients who were already deemed inoperable/unresectable,

Changes in text: We have added an addition to the discussion following your correct remarks. See changes on page 15 line 298-302 and page 19 line 378-388.

Comment 5: As the Authors stated, the issue of single-level station 5 or 6 lymph node metastasis is of lesser importance, as their impact on survival has been shown to be less important. The use of the TEMLA technique for staging purposes should be discouraged, as it is associated with unacceptable rate of complications and >20% of patients becoming medically inoperable (this has been extensively discussed in Lung Cancer journal in 2014).

Reply 5: We totally agree and have further discouraged the use of TEMLA in the discussion.

Changes in text: We added the fact that >20% of patients become inoperable after TEMLA. See page 18 line 369.

In summary, the article is valuable and provides reliable evidence. As the Authors addressed all drawbacks of their study, it also brings important matters up for discussion in the thoracic surgical and oncological community. Therefore, in my opinion, the paper deserves publication

in the Translational Lung Cancer Research.

Reviewer D

Lozekoot et al. investigated the quality of VAMLA vs. VAM. They included 301 patients undergoing VAMLA comparing to patients undergoing VAM.
The submitted paper is of good quality. The topic of the article is of great interest.

Results

Comment 1: Page 7 line 190ff: "Suspicious lymph nodes were 195 significantly (p=0.007) more often the reason to perform invasive mediastinal staging in the 196 VAM group (38% [n=45/118]) when compared to the VAMLA group (24% [n=65/269])"
I would like to ask the authors to explain why there is this gap of mediastinal staging, due to suspicious lymph nodes more precisely.
Reply 1: First, thank you for your thorough review of our manuscript and the comments raised. Secondly, suspicious lymph nodes were indeed more often the reason to perform invasive mediastinal staging in the VAM group, while a tumor larger than 3 centimeters was more frequently observed as an indication in the VAMLA group. The indication for mediastinal staging in tumors larger than 3cm was not applied compellingly during the early enrollment period (i.e., at the time when surgical mediastinal staging was performed through VAM) as this recommendation had not been embodied in the national Dutch guidelines at that time. Gradually, adherence to European guidelines (that included the indication in tumors >3cm) intensified and a shift was made to VAMLA, potentially explaining its increased frequency.
Changes in text: The preceding explanation has been added to the discussion section. See page 15 line 287-294.

Comment 2: Page 9 line 244-246
Were there any differences in complications during major lung operation following to VAM or VAMLA.
Reply 2: Unfortunately, we have not acquired data on the complications after anatomical resection. However, evaluating the difference regarding complications after anatomical resection may be of great interest for future research given the preceding differences between anatomical resection after respectively VAM and VAMLA.
Changes in text: The discussion section was amended accordingly. See page 16 line 320-329.

Comment 3: Page 9: How many different surgeons performed VAM or VAMLA?
Reply 3: Thank you for your just comment. We fully agree that your comment concerns essential information which should be available to the readers of our manuscript. The majority of VAMLAs (n=243/269) were performed by 6 distinct surgeons, while the majority of VAMs were performed by 4 different surgeons (n=92/118). The remaining procedures were performed by residents or surgeons who performed less than 10 procedures each, potentially affecting outcome.

Changes in text: The preceding has been added to the limitations section of the discussion. See page 19-20 line 394-398.

Reviewer F

The authors tried to elucidate the superiority of VAMLA compared to VAM. However, the research is based on retrospective design, and VAMLA and VAM are composed of metachronous populations. Thus, the background of each arm is so different. Furthermore, VAMLA is associated with increased risk despite its modernness, leading to inconclusive recommendations.

Major concerns:

Comment 1: The authors should rethink the design of this research which contains many biases. Even if randomized study is impractical, they should at least try to reduce the biases in the retrospective design by using multivariate analyses or propensity score matching.
Reply 1: Thank you for your critical evaluation of our submission. We understand your criticism that our current study has significant drawbacks due to its retrospective study design and the enrollment period used. Ideally, we would have performed a randomized controlled trial which is adequately powered.
Since we fully agree with your comment, the limitations section has been amended and future directions have been provided while the conclusion has been amended as well.
In addition, we have discussed the use of multivariate analyses and propensity score matching. Despite, our study comprises the largest series of VAMLAs reported to date, the sample sizes of both groups were deemed not large enough to perform matching based on different variables (including amongst others: sex, age, indication for staging etc). Moreover, for multivariate techniques to provide meaningful results they require a similarly large sample of data, otherwise the results become meaningless due to high standard errors. On advice of our statistician, we therefore used simple but straightforward statistical analysis without terms and conditions to compare both groups, allowing easy interpretation by the readers against the background of the study design's limitations.
Changes in text: The limitation section and conclusion was amended accordingly. See page 20 line 404-406, page 20 line 410-412 and page 22 line 459-460.

Comment 2: Is there any survival difference between VAMLA and VAM? Does the subtle difference in N2 detection rate affect the clinical outcome of the patients?
Reply 2: Thank you for your comment. Your question raised is of utmost importance to further clarify the discussion about the added value of VAMLA vs. VAM. Although we may observe favorable oncologic outcomes, patients eventually only benefit from an improved survival.
At current we are drafting an article concerning the disease-free survival after both VAM and VAMLA which is currently undergoing final revisions by the co-authors. Unfortunately, we can notshare this data with you due to future publication bias. Therefore, we ask for your patience and we hope to share our data with you soon via a publication.

Changes in text: No changes were made

Comment 3: What is the final recommendation in this paper, considering VAMLA is associated with higher risk of complications?

Reply 3: Thank you for your comment. The final recommendation is that VAMLA should be the preferred technique given its superior sensitivity and NPV compared to VAM for surgical mediastinal staging, however, at the cost of an increase in complications associated with VAMLA.

Changes in text: Based on your comment we feel that the conclusion could be improved in terms of clarity which has been done accordingly. See page 22 line 454-456.