Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1538

Reviewer A

Comment #1:

First of all, all incidental N2s are not same. The reason lies behind the philosiphy of surgery such as

1- When was the last imaging?

2- Did the patient undergo any invasive staging procedures such as EBUS or medx?

3- What is the uptake SUV max in the primary tumor and what is the uptake in the mediastinum?

4- How many mediastinal nodes are found to be positive intraoperatively?

5- Effects of targetted and immunotherapy as adjuvant treatment?

6 - Psychological and physiological effcets of an aborted surgery?

7- Outcomes of incidental and occult N2 disease are almost same as the outcomes of N1 disease (If intracapsular metastases, ıt can be even better).

8- Generalizing the incidental N2 disease could cause misunderstanding and could have dangerous outcomes.

9- A statistician review is a must.

Please discuss all these in the discussion in the context of İncidental N2 disease outcomes rather than N2 disease itself.

Reply #1:

Thank you for the above comments. As they all generally fall under the same thought, I will answer them all with this comment. We completely agree that N2 disease can be quite heterogeneous, but unfortunately guidelines do not differentiate the above scenarios. In the NCCN – N2 is N2 (which again, we agree there should be substantial nuance). While there have been discussions for many years about "single station N2 disease" being separate from other N2 entities, again it is not differentiated in guidelines. As far as imaging and mediastinal staging – our modeling makes the assumption that a patient had appropriate workup per other recommendations such as CT scan within 6 weeks of surgery and mediastinal staging as necessary. These are similar assumptions that are made in most retrospective NCDB and national dataset analyses that have been published in JTD and other journals when that data is not available. While I agree that generalizing patients is dangerous, guidelines are currently generalized and there are not subgroups of different types of N2 disease.

Regarding a statistician, senior author Richard Nelson is a PhD-level Health Economist who helped develop the model and analyzed the statistical methodology used in this study. An additional biostatistician would not have anything to add regarding the modeling, and are generally not included in addition to health economists in cost-effectiveness analyses as biostatisticians do not have experience in CEA modeling.

Changes in Text:

Paragraph added to discussion section emphasizing the above comments and clarifying the heterogeneity of N2 disease on lines 286-294.

Reviewer B

Comment #2:

The authors analyze the cost-effectiveness of surgical decision-making for unsuspected N2 cases by comparing two scenarios: 1) upfront surgery and 2) neoadjuvant therapy.

It is unclear what was the definition of "unsuspected" N2 by the authors. Even for the pre-operative standard nodal assessment following the current guidelines, there were about 10% of unsuspected N2 cases by final pathology made by pathologists using H.E. staining and immunohistochemistry. Even for the frozen section during surgery, some patients become unsuspected N2 due to the limitation of frozen section diagnosis during surgery.

Unfortunately, there has been no clear evidence that neoadjuvant therapy is superior to surgery with adjuvant treatment so far.

Reply #2:

As noted in our introduction, "unsuspected" N2 disease is when a patient is clinically understaged, and found to have mediastinal disease upon entry into the chest cavity. While increasingly rare as our staging improves, it can occur.

Changes in Text: None

Comment #3:

First, it is tough to consider neoadjuvant therapy for patients with unsuspected N2 disease. After the minimally invasive or invasive mediastinal staging, the incidence of unsuspected N2 is approximately 10%. Usually, unsuspected N2 is found through systematic nodal dissection and pathological evaluation using H.E. and immunohistochemistry. Did the authors mean "abort surgery" after systemic nodal dissection for all lung cancer cases?

Reply #3:

Thanks for this comment – we understand that our description was vague. As EBUS is very commonly utilized in the modern era, we agree that inaccurate nodal staging should be low. There are however situations where a EBUS was not performed, results were inconclusive, or a patient progressed between clinical staging and going for resection. In this study, aborting surgery could be after a noticeably abnormal mediastinal node is found and confirmed, or if the node looks normal but is sent for frozen confirming malignancy.

Changes in Text: Text added to discussion on lines 291-294.

Comment #4:

Did the authors routinely perform mediastinal nodal dissection and then perform lung resection? This order did not do, at least, all the data that the authors used, nodal dissection first and lung resection. Did the authors evaluate the additional cost of performing frozen sections for all surgical cases with lung cancer without evidence of unsuspected N2?

Reply #4:

Like most cost-effectiveness analyses, the model is a hypothetical based on data pulled from the literature and therefore the authors did not perform any of the procedures. Including the cost of frozen section would not impact the results of the model, as every patient regardless of outcome (abort or continue) would have frozen section performed.

Changes in Text: Text added to methods clarifying rationale for not including frozen section costs on lines 163-165.

Comment #5:
For unsuspected N2 cases, did the authors include the frozen section cost for all dissected lymph nodes during surgery, including the extension of surgical procedure and general anesthesia time?
Reply #5:
See response to comment #4. This would impact all patients regardless of decision made.
Changes in Text: None

Comment #6:
The surgery after neoadjuvant therapy for patients with post-systematic nodal dissection would be technically complicated. The surgical procedure risk cannot be equal for the patients with neoadjuvant therapy as an initial treatment.
Reply #6:
Thank you for this comment. We completely agree. This was accounted for in the model with higher risk of mortality in the group undergoing a second operation, increased operative times, and worse postoperative outcomes.
Changes in Text: Text added to methods discussing model variables accounting for increased complexity on lines 165-168

Comment #7:
There are several limitations to the decision tree. 1) Why was there not the brunch of adjuvant chemotherapy? 2) Why was there no mortality brunch for each treatment decision, including R.T., CRT, and neoadjuvant therapy? 3) There must be an operative mortality for the surgery after neoadjuvant therapy.
Reply #7:
All operative branch points include the risk of mortality. That is where the Markov Modeling comes into play. Every single treatment decision includes death as a possibility. For the operative events in the decision tree, each one also has operative mortality as an option. You don't see "operative mortality" as a branch point in the post neoadjuvant therapy resection arm as it is the final part of that treatment pathway and is built in to that decision point directly. There are unfortunately many nuances in decision-tree development and often many are not obvious on summary of the tree itself.
Changes in Text: Clarification made in methodology on line 141-142.

Comment #8:
The hypothesis of this study was based on the unrealistic clinical situation; hence, the value of the analysis itself is quite limited.
Reply #8:
While we appreciate your constructive comments above, we do not agree that it is unrealistic and should not be studied. Clinical staging is far from perfect, and even if <10% of cases, there are patients who may make it to the OR with unknowing mediastinal disease. As referenced throughout our manuscript, this has been a topic studied and published by well-known thought leaders in thoracic surgery from institutions such as Yale, University of Chicago, and NYU.

Reviewer C

Comment #9:
*Clarity and Completeness:
The abstract is well-organized and follows a logical flow of information, detailing the background, methods, results, and conclusions systematically.
Key findings and implications are also clearly stated, adding value to the reader's understanding.
Reply #9: Thank you for this comment. We put a lot of time into trying to focus the information and make it readable for those not familiar with cost-effectiveness analyses.
Changes in Text: None

Comment #10:
*Methodology:
The use of a Markov model for simulation is appropriate for this type of cost-effectiveness analysis.
The authors have also thoroughly conducted sensitivity analyses, adding robustness to the findings.
Reply#10:
Thank you – our senior author is a PhD health economist who was instrumental in developing the modeling, and has vetted our methodology.
Changes in Text: None

Comment #11:
*Results:
The results are clearly presented, showing the comparison in terms of costs and QALYs.
The incremental cost-effectiveness ratio (ICER) is a key metric in this study and has been properly calculated and interpreted.
Reply #11:
We did our best to perform an in depth cost-effectiveness analysis but make it understandable for readers of a surgical journal who may not have experience with ICER and QALY.
Changes in Text: None

Comment #12
*Conclusion:
The conclusion aligns with the results, indicating that aborting resection for neoadjuvant therapy seems cost-effective.
However, the authors appropriately suggest that continuous evaluations are necessary due to evolving treatment modalities.

*Relevance:
The paper is relevant as it addresses a critical decision in the treatment pathway of NSCLC and attempts to identify a cost-effective approach.

*Suggestions for Improvement:
It might be helpful if the authors delve a bit more into how emerging therapies, like immunotherapy and molecular testing, could impact the cost-effectiveness analysis.
Including more detailed information about the parameters and variables used in the model, and their sources, would enhance the reliability and reproducibility of the study.

Overall, this paper seems to offer valuable insights into surgical decision-making in NSCLC cases with unexpected N2 disease, contributing to the ongoing discussions on optimizing treatment strategies in oncology.

Reply #12: Thank you for the insights and constructive criticism. We completely agree that emerging therapies such as immunotherapy and molecular testing have drastically changed the landscape. This analysis was started before the use of immunotherapy was common place, and full molecular panels were standard of care. We still felt that completing the analysis and publishing our results would be useful for the literature as chemotherapy and radiation were standard adjuncts to surgery for decades, and these results and methodology could potentially lead to more in depth studies with the latest treatment strategies. Discussion on immunotherapy is important, as it is quite expensive but often very effective.
Changes in Text: Additional text added to paragraph in discussion discussing costs of immunotherapy and need to evaluate further on lines 270-274.