

Peer Review File

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Reviewer 1' comments to the authors:

Clearly and well written review. What is completely missing are some viewpoints on the surgical management of T4 disease – which patients should and which ones should not be operated on? – what is the role of induction therapy in T4 N0/N1 disease? ...

What could add more value to the manuscript would be to add a more comprehensive algorithm for the management of N2 IIIA disease: In the text you discuss bulky and non-bulky as well as single level and multilevel N2 disease – what is (or better: what should be) the implication on your decisive algorithm (Figure 1)?

Authors' reply to Reviewer 1's comments:

We thank the Reviewer tremendously for this important suggestion to discuss the surgical management of T4 disease. We have added several references discussing the feasibility of surgery, favorable disease characteristics, and the role of induction therapy in this subgroup. The pertinent discussion is in lines 176-198.

Regarding the algorithm, we appreciate the Reviewer's feedback on including additional points surrounding treatment strategies for N2 IIIA disease. We have revised Figure 1 to address this suggestion. We have also included a brief discussion on favorable vs. unfavorable characteristics in N2 disease that would influence surgical candidacy from lines 346-351.

Reviewer 2's comments to the authors:

Thank you for submitting your well written manuscript. I have some minor remarks.

Line 150-159: the study (16) showed an improved overall survival only in patients undergoing lobectomies but not after pneumonectomies. But the mortality after pneumonectomy was as high as 25%. Please comment on that. The mortality after pneumonectomies in MSKCC was 11.3% (17).

The mortality in another study was 6.8% (Pless M, Stupp R, Ris HB, et al.; SAKK Lung Cancer Project Group. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet. 2015;386(9998):1049-56).

Maybe the surgeon is a prognostic factor itself.

Line 187ff: Chemoradiation therapy as an induction therapy prior to surgery was not superior to chemotherapy followed by surgery in a study in non superior sulcus tumors. Maybe you should include this study in the manuscript.

Pless M, Stupp R, Ris HB, et al.; SAKK Lung Cancer Project Group. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386(9998):1049-56.

Authors' reply to Reviewer 2's comments:

Comment #1: Thank you for this excellent point and sharing additional references. We have included additional reports demonstrating the lower post-operative mortality rates following pneumectomy as well as a discussion of more predictors of mortality to account for the variations. Additionally, we have included findings of a study that found thoracic surgeons to have lower post-operative mortality rates following pneumonectomies than their generalist counterparts. This discussion can be found on lines 215-226.

Comment #2: Thank you for providing this additional important reference. We have now included the study by the SAKK Lung Cancer Project Group as a reference in lines 267-271 to discuss the necessity of radiotherapy when optimizing management with the available modalities.

Reviewer 3's comments to the authors:

Excellent contribution. An outstanding review article on a very complex topic of thoracic oncology; given the historical value, I would rather suggest to report and discuss the following articles that were the first two articles to examine the topic and on which almost all the guideline relies till now:

1. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst*. 1994;86:673-80.
2. Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canto A, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med*. 1994;330:153-8.

Authors' reply to Reviewer 3's comments:

Thank you for suggesting these excellent references to provide additional historical context to the role of perioperative chemotherapy. We have added these references to our manuscript and discussed the findings in lines 89-93.

Reviewer 4's comments to the authors:

Well written review. What is completely missing is the relationship between neoadjuvant molecular targeted therapy and surgery. Many studies, such as EMERGING-CTONG 1103, have indicated that median progression-free survival was significantly longer with erlotinib versus gemcitabine plus cisplatin chemotherapy as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer. The effect of neoadjuvant molecular targeted therapy or chemotherapy and surgery are well connected, which cannot be analyzed independently.

Author's reply to Reviewer 4's comments:

Thank you for your excellent feedback surrounding the relationship between neoadjuvant molecular targeted therapy and surgery. We have additionally included several trials, including CTONG 1103, EVAN, and ADJUVANT/CTONG1104, in the paper to discuss the emerging data on the use of molecular targeted therapy (EGFR tyrosine kinase inhibitors in particular). These comments can be found on lines 387-398.