

Peer Review File

Article Information: <https://dx.doi.org/10.21037/tlcr-22-345>

Reviewer A

The authors present their manuscript “Adjuvant chemotherapy for completely resected IIA-III A non-small cell lung cancer: compliance to guidelines, safety and efficacy in real-life practice”.

The authors retrospectively observed the implementation of guideline-compliant AC therapy in their patient cohort over a period of five years.

Their findings are, depending on different reasons (age, comorbidities or altered postoperative recovery) a not inconsiderable percentage of the recommended guidelines are deviated from. The authors examined which characteristics are most likely to lead to a deviation.

They conclude that AC remains efficient and well-tolerated in most patients. The reasons for application or non-application were highlighted. Therefore, according to the authors, AC therapy should be introduced as a standard in real life therapy.

First of all, the authors should please comply with the Manuscript Submission Requirements. “3.3 Text Format: Text should be double-spaced throughout.”

Reply: Thanks for your comment. We modified the text as required with double-space.

Although the manuscript is well written in terms of language and writing, I had to read it several times to get the point. No new aspects are revealed but the idea is good.

Unfortunately, it is difficult to link a real-life observational study to survival prediction and the Kaplan-Meier method.

These are two statistically different approaches which, in my opinion, cannot be reconciled. It would be nicer if the authors would consider doing two separate studies. Or to just briefly mention the part of survival that has often been described in the literature. OS or DFS must be performed with matched patient populations. Unfortunately, as the authors put it, this does not make sense.

Reply: Thanks for your comment.

We did not plan matched patient populations in the initial design of our retrospective study. First, the primary objective of this retrospective study was to evaluate compliance to adjuvant chemotherapy guidelines. Then, it is difficult to match patients' population as highlighted by reasons advanced in multidisciplinary teams for no respect to adjuvant chemotherapy compliance (See Figure 2A). As a response to your comment, we discuss the limits of survival estimation in the Discussion section as we outlined that survival of adjuvant chemotherapy group in our study might be overstated. In this context, we discussed survival obtained in previous studies for both patients who received adjuvant chemotherapy and those who underwent surgery alone. Finally, we estimated “adjuvant chemotherapy” treatment effect taking into account other patient variables in Cox multivariate analysis model.

In addition, the statistics were carried out using UICC7. UICC8 was introduced in 2017 and will soon be replaced by UICC9. Even if this means a significant additional effort for the authors, the study should be corrected accordingly. The collective should be divided according to UICC8.

Reply: Thanks for your comment.

As explained in materials and methods section, postoperative stage disease was determined according to the 7th edition of TNM classification in our study as 7th edition was recommended during patient's inclusion study period (*i.e.*, 2009-2014). At the time of our study period, the 8th edition of TNM classification was not introduced yet. All patients included in this study were classified according to 7th edition classification, that's why it could not be considered as a misclassification bias.

Was the follow-up carried out continuously? Why is no median described?

Why was the follow-up already ended in 2019 and no further patients included? This would improve the study.

Reply: Thanks for your comment.

First, as explained in the section "Efficacy and Safety profile of adjuvant chemotherapy" of Materials and Methods, we carried out a continuous follow-up within 5 years after the date of curative intent surgery for each patient included in our retrospective study. By this way, we ensured that each patient included had the same duration of follow-up.

As you carefully outlined, the follow-up ended in 2019 for patients who were included in 2014. No patients were further included after 2014 in order to ensure an equal follow-up of 5 years after curative-intent surgery. It was no longer possible to include patients later than 2014 at the time we decided to carry out this analysis.

Changes in the text: We added that the follow-up was carried out continuously in Materials and Methods (see Page 6; line 185). As it was advised, we added the mean follow-up of the study population in Patient Characteristics section (see Page 11; line 245).

These are several points of methods and statistics mentioned to encourage the authors to revise the paper. Which is very difficult, since the human factor is difficult to reconcile with statistics. There will always be more aggressive and less aggressive oncologists. The decision to use AC therapy will always be based on the willingness of the treating physicians to make decisions.

Reviewer B

I had the privilege to read the submitted paper by Désage et al. entitled “Adjuvant chemotherapy for completely resected IIA-IIIa non-small cell lung cancer: compliance to guidelines, safety, and efficacy in real-life practice”. I have to congratulate the authors on an exciting and well-written paper.

I have a few questions and minor recommendations.

Comment 1: You are using the terminology multidisciplinary team meetings (MTM). The correct English terminology is MDT multidisciplinary team. I would suggest using the correct terminology.

Reply: Thanks for your comment. As you advised, we replaced “multidisciplinary team meetings” by “multidisciplinary team” in the whole text.

Comment 2: Figure A: The authors are using different shades of blue in their analysis of reasons why chemotherapy was discontinued or never started. This journal is a color journal I would recommend using different colors, not shades.

Reply: Thanks for your comment. We corrected the figure with different colors.

Comment 3: The authors included patients in UICC stage IIIa in their analysis. Those patients in pN2 situation should have received radiation therapy as well.

I am really interested in the findings of adjuvant radiation therapy. Were there patients who received contrary to the guideline radiation therapy only?

Do the authors possess this data?

Otherwise, I would be really interested in the following paper which addresses this issue.

Reply: Thanks for your comment. This retrospective study focused on adjuvant chemotherapy and we did not address the issue of adjuvant radiotherapy in order to not mislead.

Otherwise, we also collected retrospectively patients who received adjuvant radiotherapy. In our study cohort, no patients received adjuvant radiotherapy alone. In fact, we observed that 12 pN2 patients with capsular effraction received adjuvant radiotherapy. Although small sample size, adjuvant radiotherapy was not identified as an independent prognostic factor in multivariate Cox analysis.

Post-revision Review Comments:

Thank you very much that the authors have discussed the points I raised.
Comment 1 and 2 are sufficiently answered.

Comment 3: The authors included patients in UICC stage IIIA in their analysis. Those patients in pN2 situation should have received radiation therapy as well.

I am really interested in the findings of adjuvant radiation therapy. Were there patients who

received contrary to the guideline radiation therapy only?

Do the authors posse this data?

Otherwise, I would be really interested in the following paper which addresses this issue.

Reply: Thanks for your comment. This retrospective study focused on adjuvant chemotherapy and we did not address the issue of adjuvant radiotherapy in order to not misleading.

Otherwise, we also collected retrospectively patients who received adjuvant radiotherapy. In our study cohort, no patients received adjuvant radiotherapy alone. In fact, we observed that 12 pN2 patients with capsular effraction received adjuvant radiotherapy. Although small sample size, adjuvant radiotherapy was not identified as an independent prognostic factor in multivariate Cox analysis.

Comments:

In your study, 33.8% of patients had the evidence of N2 infiltration. According to the European guidelines (Postmus et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, annals of oncology 2017), chemoradiation therapy is indicated in case of infiltration of the mediastinal lymph nodes. If you deviate from this guideline in your study group, this is of course absolutely legitimate, since radiation is very controversial. However, this should be better explained in your paper.

Reply: In guidelines referenced in the text (Kris et al. and Pisters et al.), adjuvant radiation for pN2 was considered as controversial and not recommended for routine use. As advised, we checked again the European guidelines (Postmus et al., Annals of Oncology, 2017). In these guidelines, post-operative radiation therapy was not routinely recommended in case of pN2 disease. Adjuvant radiotherapy has to be considered in case of R1 resection according to these guidelines. Patients with R1 resection were excluded from our analysis. Overall, patients who benefit from adjuvant radiation in our study were pN2 patients with capsular effraction, which is a poor histologic prognostic factor. We added a comment on postoperative adjuvant radiation in Discussion (See Page 19-20 – Line 462-466).