Peer Review File
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Reviewer A

Comment 1: Line 29 and 32: please specify whether this is range on inter-quartile range (preferable).
Reply 1: this was range
Changes in the text: we changed with inter-quartile range line 30 and line 33, as well as line 184 and line 198

Comment 2: Please do logistic regression multivariate analysis for predictors of high grade toxicity.
Reply 2: We included binary logistic regression including variables that correlated in univariate analysis with $p<0.10$ (age, ventricular ejection, concomitant radiotherapy and Charlson): no factor correlated with acute severe toxicities in multivariate analysis. No factors correlated with late severe toxicities in univariate analysis. We couldn't consequently perform multivariate analysis for this endpoint.
Changes in the text: we have added these data line 222

Comment 3: Some of the relevant meta-analysis that could be added to your discussion (PMID: 28401456 and PMID: 31088241)
Reply 3: thank you for this proposal
Changes in the text: we have added these references at line 283

Comment 4: Please spell out abbreviation in the table footnote eg NI, RT, PTV1,.etc
Reply 4: we added Legend to Table paragraph
Changes in the text: we have added these explanations at line 320

Comment 5: please add Charlson index as categories in addition to what you reported
Reply 5: done
Changes in the text: Table 1

Comment 6: please ad P value for surgery row
Reply 6: done (p=0.2)
Changes in the text: Table 2
Comment 7: Please define whether Cox regression was for OS or PFS and whether it is univariate or multivariate analysis. Please report goodness of fitess.
Reply 7: Cox regression was performed in order to determine if factors that correlated with PFS or OS in univariate analysis (Log-Rank) correlated also in multivariate analysis; since only 1 factor correlated with PFS in univariate analysis, no Cox regression was performed while 2 factors correlated with OS, so Cox regression was performed.
Goodness of fitess evaluation for Age and Charlson Index showed normal and non-normal distribution, respectively (p=0.6 and p=0.01, respectively, Kolmogorov-Smirnov test).
Changes in the text: These data were added at line 211.

Comment 8: It is advisable to report median and IQR for continuous variables and be consistent in that
Reply 8:IQR was added for all continuous variables
Changes in the text: in the whole text, Table 1 and 2

Comment 9: Please add some figures to your work eg barplots of different Charlson index in different

categories,etc.
Reply 9: Thank you for this suggestion. We have added Figure 2 which depicts barplots of Charlson index and Age as a function of type of treatment. We also have added Figure 3 which depicts barplots of Toxicities as a function of treatment type or Charlson Index.
Changes in the text: Figure 2, Figure 3

Reviewer B

Comment 1: Abstract – please explain how the analysed data lead to a conclusion that "The addition of taxanes to platinum chemotherapy was safe in the present study and warrants further exploration."
Reply 1: We observed a toxicity rate that was comparable to other studies in this setting. Indeed, we observed an acute grade 3-5 toxicity rate of 34.5% which is comparable to the 25-30% rate described by Antonia et al (ref 19) and a late 17.2% grade 3-5 toxicity rate, also comparable to the 8% rate observed by Atagi *et al* (ref 5)
Changes in the text: We have added this statement at line 280

Comment 2: Introduction – concise and well-defined background. However, I would suggest to add more background information on prediction of toxicity and currently used methods of estimating eligibility for a treatment, such as WHO performance status (PS),
Reply 2: thank you for this comment
Changes in the text: we have added the common eligibility criteria at line 65.

Comment 3: Methods
a. Staging is usually performed at the point of diagnosis. In the current study, re-staging was performed for the purposes of this study. Thus, this information should be included in the methods as well as include the references of the TNM staging and describe how the re-staging was performed (by the help of a radiologist or by a clinical re-evaluation of the CT scans?).
Reply 3: We used the 8th TNM classification for the restaging which occurred before radiotherapy, by the help of a radiologist indeed during a multidisciplinary tumor board
Changes in the text: we have added this statement at line 105

Comment 4: b. Where there any exclusion criteria? The authors exclude 26 patients due to metastatic disease, but no exclusion criteria were mentioned. If the primary outcome was toxicity prediction using Charlson index, it also could be done by including those 26 patients despite the metastatic status up-front. Please elaborate on that.
Reply 4: We only wanted to describe the outcome of combined radiotherapy and chemotherapy. Metastatic patients did not receive radiotherapy, so we had to exclude them. We also exclude patients that didn't receive radiotherapy because disease was too large.
To be clearer we have added these exclusion criteria in the Methods paragraph.
Changes in the text: the text was modified at line 90

Comment 5: c. Please explain the Charlson index in detail, as well as how the classification was performed (by a scrutinized journal evaluation, or as the index noticed in the medical history as a number, collected in the study database?). Above that, was the AIDS criteria also included? The Charlson index is partially out-dated due to the scoring of some conditions, that is no longer critical. However, the index is still in clinical use due to the lack of a better prognostic tool.

Reply 5: Yes, the AIDS criteria was also included. Charlson index was not registered prospectively in the medical history as a number. We used the version used by Quan *et al* (ref 12) which indeed removed some comorbidities from the very first version
Changes in the text: We have added a description of the Charlson index at line 75, and a detailed description of what we analyzed at line 109.

Comment 6: d. Please explain the toxicity scoring according to the 5th edition of CTCAE. This is a last edition of the toxicity evaluation and thus, the toxicity was probably scrutinized by examination of the medical histories and transferred to grading of CTCAE. The methods used to evaluate toxicity should be described in the methods.
Reply 6: Yes, the toxicity scoring was performed by scrutinizing, retrospectively, the medical history.
Changes in the text: We have added this statement at line 123

Comment 7: e. Please add if the imaging using CT or PET/CT was performed again after the sequential chemotherapy in this strategy before the radiation therapy.
Reply 7: yes we did new imaging before radiotherapy
Changes in the text: We have added this statement at line 105

Comment 8: 4. Statistical analyses
a. This section needs revision. I suggest that the sentence: "Patients' loss to follow-up (n=0) were excluded from the study" should be removed.
Reply 8: we agree and removed this sentence.
Changes in the text: sentence removed

Comment 9: How were the survival analyses performed and how the patients were divided between the groups to summarize or describe their characteristics? An online calculator is not a satisfactory tool for statistical analyses. Please find a possibility to improve the method before submitting the revised version.
Reply 9: The survival analyses were estimated via Kaplan-Meier analysis. The patients were divided between the groups to summarize or describe their characteristics via the Chi-square for categorical data and Mann-U-Whitney test for continuous variables.
We didn't use an online calculator but a professional dedicated software (SPSS version 21.0) which performs accurate statistics.
Changes in the text: These details are described in the Stastistical methods chapter at line 162.

Comment 10: b. I would argue that sample size calculation was not performed. Although it is a retrospective analysis, sample size should always be considered to understand if the scientific question can be answered using the current number of patients. If not, then longer inclusion period should be considered. It seems that the study is underpowered.
Reply 10: In this study we investigated Charlson comorbidity index as a potential predictive factor for toxicity and survival in elderly patients treated for locally advanced NSCLC. This is the first study in the entire literature to analyze this endpoint in this setting, so it was difficult to perform a sample size calculation with preliminary hypothesis. Also, we included patients during a 13-year timeframe period, the largest we could perform to retrieve comprehensive data (biology, radiotherapy).
Changes in the text: we have added details in the patient selection paragraph at line 89.

Comment 11: c. Please explain why the PS was not included in the Cox regression analyses?

Reply 11: PS was not included in the Cox regression analyses because it didn't correlate in univariate analysis with OS. PS correlated with PFS in univariate analysis but there was no other prognostic factor for PFS so multivariate Cox regression was not feasible for PFS.
Changes in the text: we detailed this statistical approach at line 173

Comment 12 : 5. Results
a. The results should include consort diagram and reasons for exclusion.
Reply 12: Done
Changes in the text: Figure 1

Comment 13: b. In the line 157, please correct to "stable disease".
Reply 13: Done
Changes in the text: corrected

Comment 14: c. There are no Kaplan-Meier curves in the results. Please consider that.
Reply 14: we created Figure 2 which focuses on the effect of the Charlson index on survival
Changes in the text: Figure 2 and at line 208

Comment 15: d. Table 3 is not informative and should be re-designed to clearly present the included data.
e. In table 3 – is the Cox regression univariate or multivariate?
Reply 15: We have redesigned the table and added Univariate and Multivariate analysis in titles to better understand the numbers; multivariate analysis was only performed for OS because there was only 1 prognostic factor in univariate analysis for PFS
Changes in the text: Table 3

Comment 16: f. Please consider to look at any differences between the centers, is the PFS, LC etc. the same? Are the treatment strategies the same between the centers?
Reply 16: One center is only doing diagnosis and surgery (CHU of Nice) while the other is doing both diagnosis and chemoradiotherapy; consequently, referral came from 2 centers but treatment (chemoradiotherapy) was performed only in 1 center
Changes in the text: we have added theses details at line 93

Comment 17: 6. Discussion
a. Please elaborate on the small sample size, why not bigger? Was there any trend towards inclusion of elderly patients in the previous years rather compared to years between 2006 and 2010? Why did authors limited the study by including only four years of inclusion period? Please explain.
Reply 17: we included patients from 2006 to 2019 (see line 27 and 89); referral of such patients might not be systematically performed by general practitioners who may think we don't want to treat elderly patients with cancer; we didn't included patients before 2006 because lack of comprehensive data; we didn't include patients after 2019 to have sufficient follow-up.
Changes in the text: we have modified the text at line 301

Comment 18: b. This is a retrospective study with its limitations. Please elaborate about the limitations of the study including the post-treatment re-evaluation of toxicity and stage of NSCLC.
Reply 18: These limitations were added in the text
Changes in the text: text was modified at line 307

Comment 19: 7. Finally, improvement of the scientific writing including language corrections should be suggested.
Reply 19: The present article was corrected by people speaking fluently in English

Reviewer C

Comment 1: 1) The abstract should highlight the study design (retrospective cohort study).
Reply 1: This was added in the abstract
Changes in the text: the text was modified at line 25

Comment 2: 2) Page 1, Line 34: Acute 3-5 toxicities should read 'Acute Grade 3-5 toxicities'
Reply 2: we corrected this error
Changes in the text: we have modified the text at line 35

Comment 3: 3) Patients were included from 2006-2019 yet were staged using the AJCC 8th edition which was published in 2017. Did authors restage all patients consistently or was staging obtained from clinical notes?
Reply 3: yes, we restage all patients using the AJCC 8^{Th} edition
Changes in the text: The text was modified at line 105

Comment 4: 4) In the introduction, it would be helpful to describe the components of the Charlson comorbidity index and expand on why it correlates with survival in NSCLC.
Reply 4: Comment partially answered upon the request of Reviewer B (Comment 5); it correlated with NSCLC because solid tumor is one of the component of the score
Changes in the text: We have modified the text at line 75 (and 109)

Comment 5: a. The cut off of 5 as a score seems arbitrary, evidence for this score should be provided or referenced, or clinical reasoning should be provided.
Reply 5: Because the predictive/prognostic value of the Charlson index is unknown in this setting we have chosen a cut-off around the median.
Changes in the text: We have modified the text at line 165

Comment 6: 5) Provide clear objectives at the end of the introduction. Currently the only objective is the correlation between Charlson comorbidity index and outcome in elderly patients. However, in other areas (and the title), the safety and efficacy of two-drug combinations was also previously listed.
Reply 6: We agree and have added this endpoint at the end of the introduction
Changes in the text: The text was modified at line 80

Comment 7: 6) Page 3, Line 133: "Patient's lost to follow up were excluded, n=0", this statement can be amended if no patients were excluded to just simply state "No patients were lost to follow-up".
Reply 7: Upon the request of reviewer B we already removed this sentence
Changes in the text: at line 164

Comment 8: 7) In the results, tumour response and survival are reported for the entire population but based on the objectives set out would be more helpful to also report rates of tumour response and survival based on whether patients received concurrent or sequential therapy.

Reply 8: we agree and have added these data; there was a better tumor response profile in favor of the concurrent strategy with however no survival benefit
Changes in the text: at line 194 and 205

Comment 9: 8) Page 4, Line 167: correct spelling for performance (also in tables as well)
Reply: we apologize for this misspelling
Changes in the text: at line 67, 127, 186, 207 and in Table 1, 3 and 4

Comment 10: 9) Similarly, toxicity data should also be reported for both patient populations rather than just the overall population.
Reply: We agree
Changes in the text: at line 239

Comment 11: 10) No comment is made on the stage category (Stage IIIA vs Stage IIIC) in the two different treatment groups as this can certainly be a deciding factor. These were also not balanced between the two groups. If a Stage IIIC patient is not a candidate for concurrent chemoRT based on extent of disease then age and comorbidity would not be of concern at first. It may make more sense to analyze Stage IIIA-B between concurrent and sequential and Stage IIIC separately (though the limited numbers make this difficult).
Reply: Yes, it make more sense but we only have 5 stage IIIC patients so the number is too small to perform relevant statistics

Comment 12: 11) In the discussion, please use the trial name (JCOG0301) or the authors rather than referring to the study as the 'Japanese trial'.
Reply: We agree and have changed the text accordingly
Changes in the text: at line 264, 277, 296

Reviewer D

Comment 1: In the introduction, the motivation for the study could be further strengthened and expand on how using the CCI to identify patients who are more likely to tolerate combined treatment can improve clinical practice. What added value does CCI provide relative to other measures such as ECOG?
Reply 1: thank you for this comment; this was already asked by Reviewer B (Comment 2 and Comment 5)
Changes in the text: at line 65 and 75

Comment 2: Line 70: Can the authors provide more details on where the "two comprehensive cancer centers" were located and the whether they are in the academic or community settings? This would help readers understand the generalizability of the study results.
Reply 2: the two centers are in the same city (Nice, France); 1 is only dedicated to the management of cancers (Centre Antoine-Lacassagne); the other is a teaching hospital which has unit dedicated to the management of cancer (CHU of Nice)
Changes in the text: at line 93

Comment 3: Lines 71-74: Please fix grammar/syntax to: "Patients were included in the study if they

had histologically confirmed advanced stage IIIA, IIIB or IIIC NSCLC, aged over 70 years, and treated with radiotherapy and chemotherapy between 12/2006 and 74 08/2019." In general, the grammar/syntax and writing throughout the manuscript could be improved. Also, check for typos (see "Performans status" in Table 1).
Reply 4: We apologize for these typos
Changes in the text: at line 78 (see also Comment 9 from Reviewer C: changes at line at line 67, 127, 186, 207 and in Table 1, 3 and 4); the present article was corrected by people speaking fluently in English

Comment 4: If the objective is to use the CCI as a predictor of patients who are able to tolerate concomitant treatment, the more appropriate design would be to evaluate only patients on concomitant treatment, and then identify predictors of patients who tolerated longer duration of concomitant treatment.
Reply 4: We fully agree and have performed new calculations; the CCI didn't correlate with PFS or OS in patients treated with concurrent strategy (p=0.9 and p=0.3, respectively); it also didn't correlate with the rate of acute and late grade 3-5 toxicities (p=0.06 and p=0.2 respectively); there was a statistical trend for concurrent treatment
Changes in the text: at line 38, 205 and 224