Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-23-176

Reviewer A

Comment 1:
In this prospective observational and retrospective cohort study with 1838 patients Real world outcome in treatment pathways for stage III lung cancer is described.
The article is well written and of high interest because of the high number of patients included.

- **Reply 1:**
  We would like to thank Reviewer A for their comments.

However I have a few questions:

Comment 2:
1) Recruited until 2019 – why no UICC Stage IIIC – please explain

- **Reply 2:**
  As stage IIIC was only introduced in the TNM staging edition released in 2017 (the 8th edition), there were no records for stage IIIC patients with acceptable data quality available in the data source at the time of this study. A sentence has been added to the Methods to explain this (line numbers 144–146).

Comment 3:
2) Interesting: 81.2% male

- **Reply 3:**
  In a previous publication focused on the Spanish Thoracic Tumor Registry (TTR) (Provencio M, et al. *Transl Lung Cancer Res*. 2019;8:461–475), the majority of patients were male (73.4%) with advanced disease. Moreover, the recent publication by Remon et al (Remon J, et al. *J Thorac Oncol*. 2021;16(2):197-204) found that the incidence of lung cancer in Spain was around 75% male. Furthermore, we have adjusted the wording in the Limitations section to acknowledge that the study population may not be fully representative of the overall Spanish NSCLC population (line numbers 272–273).

Comment 4:
3) For the stage IIIB cohort, there was a low number of initial concurrent CRT.

- **Reply 4:**
  This is stated in the Discussion: 'Concurrent chemoradiotherapy was found to be the most common initial treatment used for patients with stages IIIA and IIIB NSCLC in Spain during this period irrespective of stage or histology' (line numbers 273–275). In our study, approximately 37% of patients with stage

IIIB disease received concurrent CRT despite it being the standard of care. The reasons for this lower-than-expected use may be due to factors such as patient-specific suitability or perceptions of efficacy and safety; however, it is noteworthy that our findings are consistent with other real-world evidence studies, such as the KINDLE study, where concurrent CRT use was around 30%. This study is also described in the Discussion (line numbers 300–304).

Comment 5:

4) Page 3 line 103 European Medicine Agency (EMA)

- **Reply 5:**

  This has been updated from EMEA to EMA (line number 96).

Comment 6:

5) P6L252 Data for squamous IIIB NSCLC in neoadjuvant SACT then surgery group?

- **Reply 6:**

  Overall survival was not reached in this patient group; the manuscript wording has been updated to reflect this (line numbers 242–243).

Comment 7:

6) P7L255 Median OS for patients receiving chemoradiotherapy ranged from 28.9 to 38.9 months – why just range? Which stage? – please rephrase

- **Reply 7:**

  The stages and histology of patients in these groups have been added (line numbers 245–247).

Comment 8:

7) Please compare five-year OS rates from the Pacific trial to the mentioned 5 year os rates for neoadjuvant sact + surgery

- **Reply 8:**

  This comparison has been added to the Discussion (line numbers 339–344).

Reviewer B

Comment 1:
In this manuscript, Provencio et al. provide an overview of the real-world treatment patterns and clinical outcomes of patients with stage III non-small cell lung cancer (NSCLC) in Spain using data from the Spanish Thoracic Tumor Registry (TTR) between 2010 and 2019.
This manuscript is well written and the study is performed in a very large cohort with a considerable amount of data. The authors have performed various analyses and underlined the limitations of the study.

- **Reply 1:**
  We would like to thank Reviewer B for their comments.

Comment 2:
My main concern is the relevance and the added-value of the findings of this study in the current treatment landscape of stage III NSCLC. As also mentioned in the paper, the treatment guidelines of stage III NSCLC have been changed in the past few years and the findings do not reflect these changes.

- **Reply 2:**
  The cohort was followed until the end of 2020; therefore, these findings remain relevant as they reflect long-term treatment patterns and provide a description of treatment, management, and outcomes for patients with stage III NSCLC in Spain prior to the availability of immunotherapies. This information therefore provides a baseline upon which to evaluate the use of newer treatments as they are adopted more widely. These results are also discussed in the context of the most recent European guidelines with discussion of the change in ESMO recommendations provided in the Introduction and in the Discussion (line numbers 95–98 and 335–337).

Comment 3:
Other comments:
1. Why were patients with stage IIIC NSCLC not included in the study?

- **Reply 3:**
  As stage IIIC was only introduced in the TNM staging edition released in 2017 (the 8th edition), there were no records for stage IIIC patients with acceptable data quality available in the data source at the time of this study. A sentence has been added to the Methods to explain this (line numbers 144–146).

Comment 4:
2. What is the rationale for excluding the following patient groups? "[patients with] concomitant tumors within the five years preceding an NSCLC diagnosis except for non-metastatic, non-melanoma skin cancers and in situ or benign, neoplasms; and patients receiving any systemic anticancer therapy (SACT) within five years prior to the NSCLC diagnosis date."

- **Reply 4:**
  These criteria are added as a data cleaning step to ensure that the treatments reported are due to diagnosis of NSCLC; however, in this study no patients were excluded for these reasons therefore this sentence has been removed from the manuscript to avoid confusion (line numbers 149-153).

Comment 5:
3. Males comprise 81% of the study population. To what extent is the TTR population a true representation of the general Spanish patient population with NSCLC?

- **Reply 5:**
  In a previous publication focused on the Spanish Thoracic Tumor Registry (TTR) (Provencio M, et al. *Transl Lung Cancer Res*. 2019;8:461–475), the majority of patients were male (73.4%) with advanced disease. Moreover, the recent publication by Remon et al (Remon J, et al. J Thorac Oncol. 2021;16(2):197-204) found that the incidence of lung cancer in Spain was around 75% male. Furthermore, we have adjusted the wording in the Limitations section to acknowledge that the study population may not be fully representative of the overall Spanish NSCLC population (line numbers 272–273).

Comment 6:
4. Is patient inclusion in the TTR based on informed consent or opt-out method?

- **Reply 6:**
  Patient consent is required for inclusion in this study. A patient information sheet and informed consent is required for living patients entered in the database (prospective enrolling). If patients are enrolled retrospectively, then an informed consent is not applicable. In this study, we included both those groups of patients. This is described in the Methods section of the manuscript (line numbers 135–137).

Comment 7:
5. Based on the inclusion criteria of the study, contributing centers had to have at least 50 patients with stage III NSCLC (line 152). However, centers with less than 100 patients were excluded from the study (line 379). Please explain this inconsistency.

- **Reply 7:**
  We would like to thank the reviewer for highlighting this inconsistency. The correct figure is '100' and we have updated the manuscript accordingly (line number 146).

Comment 8:
6. Have the treatment guidelines changed during the nine-year period of data collection due to the introduction of new treatment regimens? If so, it may be that the patients

who received treatment in the first years of data collection had a different (possibly worse) prognosis than those who received treatment based on the newer guidelines. It would therefore be interesting to also indicate the change in PFS and OS in the period of data collection.

- **Reply 8:**
  Unfortunately, we do not have data to show temporal changes in PFS and OS. We have added the following wording to address these potential differences to the Limitations section …'and a change in treatment guidelines over the period of this study may mean that the prognosis for patients differed depending on when the patients were treated' (line numbers 369–371).

Reviewer C

Comment 1:
This is a comprehensive retrospective review of treatment practices in Spain for patients treated for Stage 3 NSCLC. It is a nice historical background to Stage 3 treatment in Spain but is now historical as the standard of care has changed to incorporate immunotherapy which is not represented in this population.

- **Reply 1:**
  We would like to thank the reviewer for their comments; the aim of this study was to provide a description of treatment, management, and outcomes for patients with stage III NSCLC in Spain prior to the availability of immunotherapies, and therefore to provide a real-world 'baseline' upon which to evaluate the use of newer treatments as they are adopted more widely.

Comment 2:
The included patients seem to be hugely biased to patients with excellent ECOG PS and thus I don't think really capture real treatment patterns for pts with Stage 3 NSCLC in Spain.

- **Reply 2:**
  The results presented here reflect the data as recorded in the national registry and ECOG PS is not included in either the inclusion or exclusion criteria; therefore, these data reflect the patient population during the time of this study. However, inclusion in the registry is voluntary and therefore these results may not be generalizable to all stage III patients in Spain. We have edited the following wording to the Limitations section to reflect this: 'In addition, hospitals in the GECP network have a special focus on research and inclusion in the registry is voluntary; therefore, it is likely that the largest medical centres with access to a wider range of treatment options were over-represented and that care received in these hospitals in the current study may not be representative of care received across the entire Spanish population' (line numbers 374–378).

Comment 3:
A large number of pts were excluded from the initial database. Importantly even in this highly selected group that this manuscript describes ?50% pts did not have chemotherapy, radiation or surgery? It would have been more useful if the manuscript had provided some explanations for why pts were not receiving guideline based care and also to comment on why 50% of pts were excluded. Overall although a description of pts with Stage 3 NSCLC has value; this study has included only selective pts and doesn't provide any novel insights into treatment patterns.

- **Reply 3:**
  We acknowledge that we have a large number of patients excluded from the study (51%). Patients were excluded if their diagnosis was made outside of the study period (22%), if they had poor quality data (0.5%), or were registered

with a centre that did not frequently review data completed in the TTR (not permitting study of the main outcomes – mainly patients registered in small centres <100 patients) (28.4%). We have revised Supplementary Table 3 in order to clearly define which criteria contributed to this drop in patient numbers.

The baseline characteristics of excluded patients were investigated and were found to be consistent with those in the final cohort; therefore, we believe these results are not affected by selection bias. Among the patients included, only a small number of patients (stage IIIA – 4% and stage IIIB – 6%) did not receive treatment (Table 2).

Reviewer D

Comment 1:
The present paper reported patterns of treatment and survival outcomes in patients with Stage III NSCLC in Spain. The Spanish Thoracic Tumour Registry (TTR) was used for this report. The paper is of interest for readers of TLCR. Data provided by the paper are valuable as a benchmark in the pre-durvalumab era.

- **Reply 1:**
  We would like to thank Reviewer D for their comments.

I have a few minor comments for the current version of the paper.

Comment 2:
#1. The present study included Stage IIIA and IIIB. The 8th edition of TNM system introduced Stage IIIC, which corresponds to a part of Stage IIIB in the 7th edition. Why did the authors exclude patients with Stage IIIC NSCLC?

- **Reply 2:**
  As stage IIIC was only introduced in the TNM staging edition released in 2017 (the 8th edition), there were no records for stage IIIC patients with acceptable data quality available in the data source at the time of this study. A sentence has been added to the Methods to explain this (line numbers 144–146).

Comment 3:
#2. The relationship between TTR and I-O Optimise is unclear. The title "a nationwide registry analysis from the I-O Optimise initiative" suggests the data is based on the I-O Optimise initiative, not TTR. Is this correct?

- **Reply 3:**
  A description of the I-O Optimise initiative and its relationship with European and Canadian data registry sources has been provided in line numbers 105–106 and we have amended this sentence for further clarity by adding the following wording: 'The Spanish Lung Cancer Group (Grupo Español de Cáncer de Pulmón; GECP) has recently collaborated with the I-O Optimise network in association with the ongoing nationwide Thoracic Tumour Registry (TTR) study from Spain' (line numbers 105–108). We have also removed 'from the I-O Optimise initiative' from the manuscript title to avoid any confusion and we have changed the title from 'registry analysis' to 'cohort study' for clarity.