Peer Review File

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Reviewer A:
The authors present an NCDB analysis of practice patterns and outcomes for stage 2-3 SCLC patients treated with chemotherapy and RT, with an emphasis on hypofractionated versus standard radiotherapy schedules (conventional/BID). Propensity score matching was employed. The authors report on 7143 patients and did not find a significant difference in OS in both matched and whole cohort analyses. They also determined Medicaid expansion state, metropolitan residence, and non-early CRT to be associated with HFRT use. Most interestingly, however, is that on stratification by early vs non-early CRT, they found a numerical improvement in OS for HFRT versus standard RT in non-early CRT patients, whereas the converse was true in the early CRT patients. The authors then conclude that HFRT is associated with no worse survival compared to standard RT.

Minor points:
Comment 1: Please ensure that all abbreviations are written out once in the text (e.g. MVA)
Reply 1: Thank you for your comments and for taking the time to review our article. We have reviewed and updated the manuscript to ensure that all abbreviations are now spelled out the first time they are introduced.
Changes in the text: We have modified our text as advised by writing out the abbreviations the first time they appear throughout the manuscript.

Comment 2: were variables such as PET-staging and MRI brain staging available within NCDB? if so, those could be potential variables to consider in PSM/regression models
Reply 2: Thank you for this suggestion. Unfortunately, the NCDB does not contain variables to specifically indicate if a patient received staging with PET scan or MRI. There is also no variable for invasive mediastinal staging. However, we limited our cohort to patients with known stage II-III disease according to AJCC guidelines using the following NCDB variables: **TNM_CLIN_M** ("Identifies the clinically-determined absence or presence of distant metastasis (cM) as defined by the American Joint Committee on Cancer (AJCC)") , **TNM_CLIN_T** ("Identifies the clinically-determined size and/or extension of the primary tumor (cT) as defined by the American Joint Committee on Cancer (AJCC)"), **TNM_CLIN_N** ("Identifies the clinically-determined absence or presence of regional lymph node (cN) metastasis and describes the extent of the regional lymph node metastasis as defined by the American Joint Committee on Cancer (AJCC)"), **TNM_CLIN_STAGE_GROUP** ("Identifies the applicable stage group based on the T, N, and M elements as defined by the American Joint Committee on Cancer (AJCC)"), as well as the NCDB variables for site-specific metastases at diagnosis ("CS_METS_AT_DX_[site]" and "METS_AT_DX_[site]." We have revised the methods section of the manuscript to indicate this more clearly as well as to address the lack of variables in the NCDB designating PET-staging, MRI brain staging, and invasive mediastinal staging.
Changes in the text: We have modified the text as advised to indicate the lack of NCDB variables for PET-staging and MRI brain staging and to indicate how we selected for patients with stage II-III disease. The revised text (which is found on **page 7 lines 137-143** of the manuscript in "simple markup" track changes) is shown below, highlighted in yellow:

Patients with stage I disease were excluded due to radiotherapy treatment primarily with stereotactic body radiotherapy, which is beyond the scope of this study. The NCDB does not contain variables to indicate positron emission tomography (PET) staging, magnetic resonance imaging (MRI) brain staging, or invasive mediastinal staging. We used the NCDB variables for clinically determined T stage, N stage, M stage, overall TNM stage, and site-specific metastasis to select for patients with stage II-III disease.

Comment 3: another institutional series utilized propensity score methods and found comparable outcomes between HFRT and BID (https://www.mdpi.com/2072-6694/13/12/2895)
Reply 3: Thank you for referring us to this relevant and important study. In addition to their overall survival results being consistent with ours, it is interesting that there were no differences in locoregional recurrence risk, thoracic response, or ≥grade 3 toxicity. We have now cited this study in our manuscript and have included a brief discussion of the study as well in our discussion section.
Changes in the text: We have now cited this study in our manuscript and have included a brief discussion of the study as well. The revised text with corresponding page and line numbers (in "simple markup" track changes) is shown below, highlighted in yellow:

Page 6 line 115: Additionally, some smaller institutional studies have found comparable or occasionally improved locoregional control and/or survival without significantly increased toxicity with HFRT compared to standard RT in this setting (11-19).
Page 18 lines 388-393: Similarly, Yan et al. performed an PSM-adjusted bi-institutional retrospective analysis comparing HFRT (40 Gy/15 fractions) with accelerated RT (45 Gy/30 BID fractions) using with overlap weighting for clinical and treatment variables; among the 173 patients included in their analysis (63 HFRT and 110 accelerated RT), there were no significant differences in OS, thoracic response, locoregional recurrence risk, or grade 3+ toxicity (19).
Page 28 line 631: 19. Yan M, Sigurdson S, Greifer N, et al. A Comparison of Hypofractionated and Twice-Daily Thoracic Irradiation in Limited-Stage Small-Cell Lung Cancer: An Overlap-Weighted Analysis. Cancers (Basel). 2021;13(12):2895. Published 2021 Jun 9. doi:10.3390/cancers13122895

Comment 4: In discussion on page 14, line 359, the authors suggest that standard RT may be associated with greater toxicity (compared to HFRT), however most studies (RCT or observational) suggest similar rates.
Reply 4: Thank you for bringing this to our attention. Given the comparable toxicity between HFRT and standard RT demonstrated in many of the studies cited in our manuscript, we have now removed this statement from the discussion section.
Changes in the text: We have modified our text as advised by removing this statement from the discussion. The revised text with corresponding page and line numbers (in "simple markup" track changes) is shown below, highlighted in yellow:

Page 21 lines 466-469: This is particularly relevant during the COVID-19 pandemic, during which treatment delays and increased logistic barriers to travel are not uncommon. [DELETED: ~~Moreover, one might also consider the cost in terms of the toxicity associated with a full course of standard RT in patients who are unable to benefit from early administration of chemotherapy.~~] The relationship between fractionation schedule

and timing of chemotherapy, and its impact on survival, should be prospectively explored.

Comment 5: discussion page 14, line 373, what are some examples of confounders you think may not be capitulated in the NCDB?
Reply 5: Thank you for this comment. We think that the following could be possible confounders of overall survival not included in the NCDB: tumor location beyond laterality (specifically, central vs. peripheral tumor location), ECOG performance status, smoking status, imaging modality used for staging (including PET-staging and MRI brain staging), and number of chemotherapy cycles received. We have now included these in the discussion.
Changes in the text: We have modified our text as advised by adding the confounders listed in our response in the discussion. The revised text with corresponding page and line numbers (in "simple markup" track changes) is shown below, highlighted in yellow:

> **Page 22 lines 484-491:** Still, there may be unmeasured confounders from certain characteristics not included in the NCDB, including central vs. peripheral tumor location, performance status, smoking status, number of chemotherapy cycles received, and more specific information regarding modalities used in staging such as PET imaging, brain MRI, and invasive mediastinal staging (15, 19). The non-early concurrent chemotherapy group could potentially represent a less favorable population based on these confounders, contributing to the correlation with HFRT in this group and perhaps limiting the generalizability of our results.

Reviewer B:
This manuscript evaluated treatment outcomes with hypofractionated radiotherapy in locally advanced limited-stage small cell lung cancer comparing with standard radiotherapy ,using the National Cancer Database. This paper is well discussed. Also, I think that this study would be a valuable study in this field. However, there are some issues to be resolved in this manuscript described below.

Comment 1: The authors should mention UICC edition of the classification the target patient has been diagnosed with.
Reply 1: Thank you for your comments and for taking the time to review our article. We have now referenced the AJCC/UICC edition used to classify the study population (6^{th} edition AJCC/UICC for patients diagnosed between 2008-2009 and 7^{th} edition for patients diagnosed between 2010-2016.
Changes in the text: We have modified our text as advised by referencing the AJCC/UICC edition used to classify disease stage in our study population. The revised text with corresponding page and line numbers (in "simple markup" track changes) is shown below, highlighted in yellow:

> **Page 6-7 lines 133-137:** All patients were diagnosed between 2008-2016 with primary locally advanced LS-SCLC (stage II-III) according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging guidelines based on year of diagnosis (6^{th} edition for patients diagnosed in 2008–2009, and 7^{th} edition for patients diagnosed in 2010–2016).

Comment 2: The authors should mention the follow-up period of each group.
Reply 2: Thank you for your comment. We had included the follow-up periods for both HFRT and the standard RT groups for both our propensity score matched analysis as well as our analysis involving the entire cohort; however, we did not include follow-up periods for our subset or sensitivity analyses. We have now included the follow-up periods of each group (HFRT and standard RT) for all subset and sensitivity analyses.
Changes in the text: We have modified the text as advised, including the follow-up periods of each group (HFRT and standard RT) for all subset and sensitivity analyses. The revised text with corresponding page and line numbers (in "simple markup" track changes) is shown below, highlighted in yellow:

- **Page 13-14 lines 296-298:** Median follow-up times for those who received standard RT and those who received HFRT among all patients in the early concurrent chemotherapy subset were 51.2 [CI 49.2-52.8] and 53.3[CI 37.1-71.2] months, respectively.
- **Page 14 lines 305-308:** In this matched early concurrent chemotherapy subset, median follow-up times were 45.5 [CI 32.3-77.0] months for patients who received standard RT and 47.5 [CI 32.1-74.7] months for patients who received HFRT.
- **Page 14 lines 315-318:** The median follow-up times in the non-matched non-early concurrent chemotherapy subset were 59.8 [CI 55.7-65.1] and 62.8 [CI 41.1-79.5] months for patients who received standard RT and HFRT, respectively.
- **Page 15 lines 323-325:** The median follow-up times for patients in this non-early concurrent chemotherapy matched subset were 52.4 [CI 38.7-72.6] and 62.8 [41.1-79.5] months for those who received standard RT vs. HFRT, respectively.
- **Page 15 lines 335-337:** Median follow-up times in this subset were 51.9 [CI 50.6-53.6] and 55.1 [CI 40.7-71.2] months among patients who received standard RT and HFRT, respectively.
- **Page 16 lines 342-343:** Median follow-up times in this matched subset were 59.4 [39.3-76.8] and 55.1 [CI 40.7-71.2] months among patients receiving standard RT vs. HFRT, respectively.
- **Page 16 lines 348-350:** Median follow-up times in this subset were 62.3 [CI 55.7-69.7] and 71.6 [CI 41.1-.] months among patients who received standard RT and HFRT, respectively.
- **Page 16 lines 354-356:** Median follow-up times in this matched subset were 59.4 [CI 42.5-83.2] and 71.6 [CI 41.1-.] months for patients receiving standard RT vs. HFRT, respectively.

Comment 3: There is a big difference in the number of target groups, as described by the author as limitation. In this propensity score matching, many of the patients in the standard group are not eligible for testing, and we believe that the bias is very large. Comparison after propensity score matching is one reference, but at this point, we believe that comparison of the original data may be a more robust indication of outcome.
Reply 3: Thank you for your comment. We had originally decided to use the propensity score matched analysis as our primary analysis given the large differences in numbers between the

HFRT and the standard RT group with the potential for small sample bias. However, we agree that the large number patients that are excluded from the standard RT group likely introduces significant bias as well and that the comparison of the original data may be a better indicator of the outcome. Thus, we have revised the manuscript such that the analyses involving the whole cohort is the primary analysis and the propensity score matched analyses are the sensitivity analyses.

Changes in the text: We have modified our text as advised by making the analyses on the whole cohort the primary analysis and making the propensity score matched analyses a sensitivity analysis. This is now reflected in the methods, the reporting order of the results, and the order of the tables and figures. The revised text with corresponding page and line numbers (in "simple markup" track changes) is shown below, highlighted in yellow:

- **Page 8-9 line 179-199:** order of paragraphs has been switched
- **Page 9 lines 186-187:** Propensity score matching (PSM) analysis was performed as a sensitivity analysis to reduce the effect of possible known confounders on OS outcomes.
- **Page 9 lines 200-201:** We performed survival analysis in both our original, non-matched cohort as well as our PSM cohort.
- **Page 12 line 266:** Survival Outcomes in All Patients and Matched Cohort
- **Page 13 line 276:** On sensitivity analysis involving the PSM cohort (N=292), median follow-up time for patients who received standard RT was 59.7 months (CI 43.1-77.0) compared to 56.6 months (CI 43.9-71.6) in patients who received HFRT.
- **Pages 12-16 lines 266-356:** order of presentation of PSM and whole cohort data switched so that whole cohort data presented first.
- **Page 17 lines 368-370:** While median OS was more than six months longer with standard RT compared to HFRT among the non-matched subset of patients who received early concurrent chemotherapy, median OS was eleven months shorter with standard RT compared to HFRT among the non-matched subset who received non-early concurrent chemotherapy.
- **Page 20 lines 437-441:** Interestingly, our analysis demonstrated worsened OS with HFRT compared to standard RT among those who underwent early concurrent chemoradiation, but improved OS with HFRT compared to standard RT among those who underwent non-early concurrent chemoradiation, although neither of these findings quite reached statistical significance in our matched sensitivity analyses.
- **Page 33 lines 725-744:** order of graphs switched:
    - Figure 2. (a) Overall survival comparison with 60 months follow-up by type of radiation received (standard radiation [standard RT] vs. hypofractionated radiation therapy [HFRT]) among the whole cohort (N=7,143). (b) Overall survival comparison with 60 months follow-up by type of radiation received (standard radiation [standard RT] vs. hypofractionated radiation therapy [HFRT]) among the propensity score matched cohort (N=292).
    - Figure 3. (a) Overall survival comparison with 60 months follow-up by type of radiation received (standard radiation [standard RT] vs. hypofractionated radiation therapy [HFRT]) among the non-matched subset of patients who

received non-early concurrent chemotherapy (N=5,137). (b) Overall survival comparison with 60 months follow-up by type of radiation received (standard radiation [standard RT] vs. hypofractionated radiation therapy [HFRT]) among the propensity score matched subset of patients who received early concurrent chemotherapy (N=138).

  - Figure 4. (a) Overall survival comparison with 60 months follow-up by type of radiation received (standard radiation [standard RT] vs. hypofractionated radiation therapy [HFRT]) in the non-matched subset of patients who received non-early concurrent chemotherapy (N=2,006). (b) Overall survival comparison with 60 months follow-up by type of radiation received (standard radiation [standard RT] vs. hypofractionated radiation therapy [HFRT]) in the propensity score matched subset of patients who received non-early concurrent chemotherapy (N=154).

- **Table 1:** Univariable and multivariable Cox regression analysis for variables potentially associated with overall survival in non-matched (all) patients (N=7,143) and matched patients (N=292).
- **Table 2:** Univariable and multivariable Cox regression analysis for variables potentially associated with overall survival in non-matched patients (N=5,137) and matched patients (N=138) who received early concurrent chemoradiotherapy.
- **Table 3:** Univariable and multivariable Cox regression analysis for variables potentially associated with overall survival in non-matched patients (N=2,006) and matched patients (N=154) who received non-early concurrent chemoradiotherapy.

Reviewer C:
The manuscript was well written and scientifically interesting. In my opinion, it is almost acceptable; however, there are several questions to be answered.

Comment 1: 1. Patients in the HFRT group were more common in the academic centers and they were prone to receive non-early concurrent chemotherapy. It seems that HFRT is performed mainly on the clinical trial basis and it is not recommended to give HFRT and chemotherapy concurrently in the protocol. Do you have any information on that?
Reply 1: Thank you for your comments and for taking the time to review our article. We think that HFRT is mostly given off study as it is not standard of care and speculate that physicians at academic centers may be more willing to prescribe less standard therapy in this setting, accounting for both the low numbers of HFRT in our study as well as the association between HFRT and treatment at academic centers. We are not aware of any ongoing U.S. clinical trials comparing HFRT with standard RT in this setting, but if there are any specific trials that you believe should be mentioned in the manuscript, we would be more than happy to cite/discuss them in our revised paper.
Changes in the text: We have not made any specific revisions in the text based on this comment as we are not aware of any U.S. clinical trials specifically comparing HFRT vs. standard RT in

this setting, but we are more than happy to cite/discuss any clinical trials the reviewer feels should be mentioned in the paper.

Comment 2: 2. The conflicting results of the subgroup analysis (HFRT vs standard RT) based on the timing of chemotherapy was impressive. But, the authors did not mention any scientific background on these results. Do you have any speculation on that?
Reply 2: Thank you for this comment. We briefly mentioned the time interval between start of any treatment until the end of radiation as a potential reason for the improvement in survival associated with HFRT in our non-early concurrent chemotherapy group in the fifth paragraph of the discussion; however, we have now added a more substantial discussion of the scientific background potentially explaining our conflicting results in the chemotherapy subgroup analysis. Specifically, we have now discussed performance status, group selection, toxicity and biologically effective dose, and radio-sensitization as potential reasons for our subgroup analysis results.
Changes in the text: We have modified the text as advised, providing more scientific background on the conflicting results of our chemotherapy timing subset analyses – specifically, we have now added to the discussion how performance status, group selection, toxicity and biologically effective dose, and radio-sensitization could serve as potential reasons for our subgroup analysis results. The revised text with corresponding page and line numbers (in "simple markup" track changes) is shown below, highlighted in yellow:

> **Pages 20-21 lines 447-461:** Moreover, the group of patients who received early concurrent chemotherapy (the preferred timing for chemotherapy) along with standard RT may represent a group with better performance status compared to those patients who were selected to receive non-standard therapy. This former standard treatment group may have benefited from a full course of standard RT, whereas patients who received HFRT and sequential chemotherapy may have been ineligible for early concurrent chemotherapy based on performance status or disease burden. In these patients, less aggressive RT with a lower biologically effective dose and possibly less toxicity may potentially be beneficial. Additionally, without the benefit of radio-sensitization with early concurrent chemotherapy, a shorter course of radiation treatment (with a shorter SER) may account for the improved survival with HFRT in the non-early concurrent chemotherapy subset. However, the relationship between chemotherapy timing and fractionation schedule in LS-SCLC must be studied in greater detail, with future prospective studies stratifying patients based on timing of concurrent chemotherapy in this setting.