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Reviewer A

Your manuscript provides valuable insights in the thoracic surgical field. I have some suggestions that could potentially improve the paper:

- In Table 2, a summary of each study could be inserted in the column "Comment"

Reply: The major conclusion has been added to each meta-analysis included in Table 3 (previously Table 2).

Changes: Final column titled "Conclusions" and broad conclusions were added. The first two are listed here: (1) Conforti, 2018: "Advanced or metastatic cancers were studied, of which NSCLC was a subgroup. In the overall study of 20 trials and 11351 patients, pooled male survival was 0.72 (0.65 – 0.79) and female survival 0.86 (0.79 – 0.93) with a significant difference in efficacy between sexes ($p = 0.0019$), demonstrating sex-specific benefit in overall survival with ICI therapy." (2) Conforti, 2019: "Females with advanced NSCLC derive greater benefit from combination chemoimmunotherapy than males, though both demonstrate improved survival with combination therapy over chemotherapy alone. However, only males demonstrate benefit from anti-PD-1 alone over chemotherapy." And so on.

- As I reported in a previous study, "Despite positive post-operative results, studies documented that the appropriate lung resection is performed less frequently in women than in men, in terms of the timing and extension of resection [1]". This issue should be discussed in the section regarding the surgical treatment.

[1] ZIRAFÀ, C., ROMANO, G., SICOLO, E., CASTALDI, A., DAVINI, F., MELFI, F.. Lung cancer surgery in women: focus on gender-related outcomes—a narrative review. *Precision Cancer Medicine, North America*, 6, feb. 2023

Reply: Thank you for bringing this article to my attention. The sources cited in the above article were reviewed and are now discussed in the final paragraph of that section.

Changes: "Studies have demonstrated sex disparities in surgery for early-stage lung cancer. A review of patients with Stage I NSCLC who participated prospectively in the National Lung Screening Trial found that women were "less likely to undergo full resection" despite having surgery as often as men, though this was not statistically significant. The authors posited favorable pathology and patient preference may have influenced these decisions. An early comparison of limited resection versus lobectomy for Stage IA lung cancer showed that limited resection was performed in females more often, though we now have robust evidence that sublobar resection is non-inferior to lobectomy in patients with clinical stage IA peripheral NSCLC tumors less than two centimeters. What was previously considered a limited resection is now known to be a suitable choice in select patients.

- There are some typing errors in the paper. Please, check it.

Reply: Spelling, grammar, and punctuation were reviewed carefully.

Reviewer B

This narrative review performed by K. Gee and S. Yendamuri explores the often-overlooked role of biological sex in lung cancer, historically considered a male disease. Disparities in lung cancer incidence are now primarily driven by females, especially non-smokers and the young. The review covers exposure-related risk factors, hormonal influences, screening guidelines, immune system responses, and treatment outcomes, emphasizing the need for further study to eliminate disparities and improve treatment for both sexes.

Minor changes:

* In the abstract it is stated: “What is clear is that the female immune system reacts more aggressively to lung cancer, and females ultimately have superior outcomes”. -> This statement seems to suggest that the better prognosis in women is only due to their immune response. Since other factors, such as lifestyle (non-smokers), may be influencing women's better prognosis, I think the statement should be toned down a bit.

Reply: Thank you for this comment. My use of punctuation and phrasing did not appropriately reflect the intended meaning.

Changes: “The effect of biological sex on carcinogenesis and the immune system response to cancer is not fully understood, though the female immune system clearly reacts more aggressively to lung cancer.”

* In the section SCREENING AND DIAGNOSIS-> “This may suggest that smokers of either sex are less likely to seek medical opinion when faced with symptoms concerning for lung cancer” -> I would suggest consider to add a comment to this article (1), which analyzes whether there are differences between men and women in the diagnostic presentation of lung cancer. They found that weight loss/anorexia/asthenia was the most frequent symptom in both sexes and there were no differences in the number of symptoms at diagnosis. There were no relevant differences in the frequency or number of symptoms by sex when non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) were analyzed separately.

Reply: This article was originally excluded as it didn't find notable differences in clinical presentation between men and women. I have now added its findings to the Screening and Diagnosis section.

Changes: “Moreover, a study in Spain found no clinically relevant differences in symptoms at diagnosis between patients of either sex or variable smoking status (43), highlighting that healthcare providers must remain vigilant when determining patients who may benefit from lung cancer screening.”

Reference:

1) Ruano-Ravina A, Provencio M, Calvo de Juan V, et al. Are there differences by sex in lung cancer characteristics at diagnosis? -a nationwide study. *Transl Lung Cancer Res.*

Reviewer C

This is an excellent summary of the literature available on lung cancer and sex disparities. The authors do an outstanding job of integrating the studies found in the search and organizing them into sections. However, I noticed a few issues that need to be resolved to improve the quality of the study:

- 1- I suggest editing the title, removing the words "differences in", or adding males, otherwise it is unclear what differences the title refers to

Reply: Title edited.

Changes: "Lung Cancer in Females – Sex-Based Differences from Males in Epidemiology, Biology, and Outcomes: A Narrative Review"

- 2- on line 78 in the introduction, the sentence about the CDC incidence needs to be revised...it states a reduction from 2020 to 2019? I believe the years are reversed. Please revise this sentence.

Reply: The sentence compares lung cancer incidence in 2000 and 2019. No changes made.

- 3- the introduction can have a little more background about differences in males and females, as well as the average age of diagnosis for both sexes

Reply: Statements about sex-specific incidence and mortality have been added.

Changes: "In recent years, lung cancer incidence has been 27% higher among males compared to females, though both incidence and mortality are declining more rapidly in males than females." And "Its (NSCLC) incidence peaks at ages 80 to 84 in males compared to 75 to 79 in females."

- 4- methods: please detail the inclusion and exclusion criteria used to select the articles to be included in the study

Reply: Details added.

Changes: "The primary author reviewed the titles and abstracts of the 196 articles delivered. Articles of poor reliability or those that examined especially geographically-specific lung cancer trends were excluded. The authors considered sixty-two publications germane to the themes of this review and their full texts, including references, were studied in detail."

- 5- line 215, please correct the typo in the section title: "Diagnosis", not diagnosis

Reply: Section title corrected

Changes: "**SCREENING AND DIAGNOSIS**"

- 6- line 370, please define "IA"

Reply: Defined at its first usage.

Changes: “For example, stages III and IV conferred a HR 8.71 for female patients versus 3.66 for male patients compared to the reference group which was comprised of patients diagnosed at Stage IA, meaning their tumors were less than three centimeters.”

- 7- Table 1 should have the list of articles that were selected for the study. It is unclear which ones were included in the listed references. Please add a table that lists the articles found for each subheading that is mentioned in the results. How many of the 63 selected articles are in Table 2? How each article was used and how many were relevant to each section needs to be at least mentioned.

Reply: I have included a table (Table 2) that lists the citations in the format of “Author, PMID” used in each section of the results. This format was used for brevity, as readers can use the references to find further information.

- 8- the conclusion is not specific, does not summarize what is learned from the review, and has several grammatical issues. I suggest re-writing this section.

Reply: Thank you for this feedback. The conclusion has been rewritten.

Changes: Increasing lung cancer incidence in non-smokers and young females begs demands greater understanding of sex-based drivers of the disease. Environmental exposure studies, especially those which examine risk factors present in the home, are lacking, the effect of sex hormones on carcinogenesis in the lung is not well understood, and females continue to be underrepresented in clinical trials for lung cancer treatment. Randomized controlled trials with uniform control arms are necessary to truly optimize treatment regimens with new systemic therapies. Practically-speaking, clinicians must recognize that current screening guidelines do not reflect the changing demographics seen in new lung cancer diagnoses. Further investigation into the sex-specific differences in lung cancer will not only increase the proportion of patients diagnosed in its early stages, but also generate sex-based treatment modalities.

Reviewer D

This paper is a narrative review on the differences in lung cancer regarding females. This manuscript could be improved by the implementation of the following:

Introduction

- Missing references on pages 2-3, lines 77-84.

Reply: Unfortunately, the lines cited do not match my document. I presume the reviewer was referencing the below information, which was all obtained from the CDC’s US Cancer Statistics Data Visualization tool.

Changes: “The Centers for Disease Control and Prevention reports the mortality rate of lung cancer was 55.8 per 100,000 people in 2000 but has now decreased to 33.4 per

100,000 people as of 2019, the most recent year for which reliable data is available (4). Likewise, the incidence of lung cancer has declined from 70.2 to 54.3 per 100,000 people, though the actual number of new lung cancers has generally increased over that period due to a growing population (4). Noticeably fewer new cases were reported in 2020, thought to be tempered by the unprecedented impact of the COVID-19 pandemic on health services and recommended screening practices (4).

- Authors could emphasize and spend more time in this section talking about the problem and the gap in the literature instead of/ in addition to the statistical facts.

Reply: I appreciate this suggestion, and I agree. Redundant statistics on mortality were removed in the first paragraph of the introduction and comments on the gap in literature have been added in the second paragraph.

Changes: “Importantly, disparities in lung cancer incidence largely depend on increasing rates of adenocarcinoma driven by young females and never smokers (8) yet understanding of this demographic shift is sorely needed. Consensus on lung cancer risk from non-tobacco exposures, the influence of sex-specific hormones, and sex-based immune response to carcinogenesis are ill-defined in the literature.”

Methods

- The authors only used one database which could increase the risk of bias in this study.

Reply: Yes, only PubMed was used. More explicit limitations of the review are now detailed for full transparency.

Changes: “The limitations of this narrative review must be acknowledged. A single database was used to collect relevant literature, and articles were selected based on relevancy as determined by the authors’ expertise. Our review is not an exhaustive examination of all data published on this topic.”

- The authors do not mention MeSH terms used for their search and methodology.

Reply: MeSH terms were not used for searching PubMed.

- Missing quality assessment of the articles included.

Reply: More specific criteria have been added.

Changes: “Articles of poor reliability or those that examined especially geographically-specific lung cancer trends were excluded.”

- Missing Inclusion and exclusion criteria for the articles.

Reply: More specific criteria have been added.

Changes: “Articles of poor reliability or those that examined especially geographically-specific lung cancer trends were excluded..”

- This section needs work.

Risk factors

- Other risk factors unique to the female population are not considered. The authors could talk about the exposure to secondhand smoke more widely, cultural influences (like indoor coal/wood burning mechanisms to cook), occupational exposures, etc.

Reply: Additional information about secondhand smoke and culturally-related exposures have been added.

Changes: “Exposure to second-hand smoke, more commonly experienced by women, increases the risk of lung cancer. An observational study of non-smokers with lung cancer found 69% of females experienced environmental tobacco smoke exposure, compared to only 17% of males. Interestingly, males in this study reported exposure only at work, while females experienced exposure at home and work. As detailed by Baiu et al. in their recent discussion on gender in NSCLC, known risk factors such as asbestos and radon have been particularly poorly studied in women, though women spend more time in the home and consequently have greater exposure to indoor pollution including radon and tobacco smoke residues that persist on indoor surfaces, termed thirdhand smoke. A recent meta-analysis found cooking factors, including fume and coal smoke exposure, conferred the highest lung cancer risk to non-smoking Asian women (odds ratio [OR] 2.15, 95% CI 1.87 – 2.47) among pooled risk categories of personal and family history, environmental tobacco exposure, diet, and reproductive factors. Female chefs exposed more intensely and for more years to cooking oil fumes, which contain known carcinogens, had a significantly higher risk of lung adenocarcinoma compared to male chefs and those less often exposed to cooking oil fumes due to specific cooking practices.”

Reviewer E

This manuscript is a narrative review that summarizes sex-specific characteristics of lung cancer, highlighting risk factors, diagnosis patterns, carcinogenesis, and treatment outcomes in females. The rationale and key questions for the narrative review are clear and compelling. The manuscript is well written and well organized. Relevant studies are included, and key findings and limitations of these studies are clearly stated. Overall, the narrative review is important and deserving of publication. However, there is one concern that should be addressed before the manuscript is accepted for publication: in the Outcomes section, the authors nicely summarize differences in surgery for early-stage lung cancer, targeted therapy, and immunotherapy. However, there is no discussion about differences between females and males in responses to conventional platinum-based chemotherapy or radiation therapy (e.g., SBRT), which remain important treatment modalities for NSCLC.

Reply: We certainly agree that SBRT and traditional chemotherapy are important modalities in lung cancer treatment. However, we felt covering these topics in depth was outside of the scope of our review. We wanted to focus on the role of curative surgery (as we are surgeons) and sex-specific differences seen in the newer systemic therapies. I have clarified our scope in the second paragraph on outcomes, as well as included a general statement on what is known about sex-based differences in the treatment of advanced

NSCLC with radiation and chemotherapy.

Changes: “This review will concentrate on sex-based differences in outcomes of surgery, the favored management of early disease, and contemporary systemic treatments.”; “A previous meta-analysis of patients with inoperable NSCLC treated with radiation therapy found that female gender was the sole demographic factor to confer an overall survival benefit. In contrast, a large retrospective study of patients who underwent stereotactic body radiation therapy found that unfavorable histology, increased body mass index, significant comorbidities, and radiation dosing were predictive of local treatment failure, but not sex.”; “In comparison, older studies demonstrate that traditional chemotherapy offers marginal benefit (on the order of months) to females over males in certain subgroups.”