

Peer Review File

Article information: <http://dx.doi.org/10.21037/jtd-20-3128>.

Reviewer A:

The manuscript provides an excellent review of a very under-appreciated topic - gender issues in thoracic malignancies. Please see below for comments.

Comment 1: This is a very well-written review. This is merely a suggestion, but nice Tables and Figures summarizing the findings will make the readers want to refer back to the review, which the current work lacks. Could the authors make a Table listing the gender-specific differences that is so nicely outlined in their work? I think such summary Table would make this manuscript even better.

For example:

- a. For lung cancer screening, authors list out issues such as women not meeting current criteria (due to more non-smoker women having at risk for cancer) and how other risk factors are more commonly found in women.
- b. For molecular differences in lung cancer, authors point out that EGFR mutation is more commonly found in women.
- c. For lung cancer surgery, authors point out that women are less likely to receive definitive surgery.

If the authors could expand on the factors listed out in Figure 1 and Table 1 (add details and references), this would make a much more meaningful Table. As they are, the Table and Figure are very generic and not particularly novel to the findings that is so nicely reviewed in their work.

Reply 1: Thank you for this suggestion. We agree that visual aids can be helpful and have struggled with an effective way to summarize a narrative. Furthermore, reviewer C suggested removing both the figure and the table. In light of this, we have elected to delete both of them as they did not provide any additional information from what is otherwise presented in the text. We are however open to any other suggestions.

Comment 2: There are a couple grammar suggestions:

- a. Page 8, Line 5 - “predictors of lung” should be “predictors of lung cancer”?
- b. Page 11, Line 3 – “blind” should be “blinded”.

Reply 2: Thank you. These have been revised.

Comment 3: Does reference 61 regarding Osimertinib have gender-specific implications? Other studies cited in this paragraph are EGFR-related studies that showed some gender-specific differences.

Reply 3: You are correct, reference 61 does not have direct gender-specific implications. We included this reference in order to highlight the utility of targeting EGFR as part of multimodality treatment therapies.

Reviewer B:

Comment 1: Please revise the following paragraph as there are clear guidelines for surveillance of Barrett's patients to identify cancer. And there are guidelines for a baseline EGD in high-risk groups (men >50 with frequent GERD, etc). Maybe just temper the message here: "The utility of screening for esophageal cancer in patients with Barrett's esophagus and/or symptoms of gastroesophageal reflux disease (GERD) is still debated in the literature. Although there is a clear pathway of GERD leading to Barrett's and esophageal adenocarcinoma, endoscopic screening has not been associated with a reduction in cancer-related mortality and therefore screening is not formally recommended."

Reply 1: We have modified the sentence to now say "*There are well established screening guidelines for esophageal cancer in patients with Barrett's esophagus and/or symptoms of gastroesophageal reflux disease (GERD). However, the adherence to these guidelines is variable, and similar to lung cancer, worse for women compared to men patients (56).*" (Revised manuscript page 10)

Comment 2: There are some grammar/typo changes

- a. Introduction: "This manuscript provides a review on the role of gender plays in the diagnosis...", of should be changed to that.
- b. MEDICAL THERAPY FOR THORACIC MALIGNANCIES "Several trials have noted increased side effects as nausea, vomiting, alopecia, neurosensory toxicity, severe hypertension, constipation, abdominal pain in women compared to men.(31)" severe hypertension should be changed to severe hypertension
- c.
- d. SUMMARY "As oncologic care is advancing towards individualized approaches to..." towards should be changed to toward

Reply 2: These have been revised.

Reviewer C:

Thank you for the opportunity to review this paper. The role of gender in the treatment of thoracic malignancies is undoubtedly a critical topic considering the current scenario where we see, in the clinical practice, that gender can have significant implications in the diagnosis, management, and prognosis of patients. The number of non-smoker females with

adenocarcinomas (frequently found at early stages) diagnosed early in life is becoming more prevalent in current practice. Indeed, gender will play a significant role in all aspects of the management of Primary Lung Cancer. Considering this is a review paper, we will write our review on an item per item fashion.

Comment 1: Title: We believe the title can be focused to more accurately reflect the content to the readership to something suggested as follows: “The role of gender in non-small cell lung cancer: a systematic review”.

Reply 1: We agree with this suggestion and have revised the title to narrow our focus.

Comment 2: Abstract: We think you addressed what you planned to review.

Reply 2: Thank you

Comment 3: Introduction: Your rationale makes sense, but you write basically about lung cancer and a bit about esophageal cancer. Do other tumors like mediastinal, pleural also can have potential gender implications. We think it would be essential for you to explore; otherwise, maybe a good suggestion would be to restrict your title to “lung cancer” instead of “thoracic malignancies.” Please revise the introduction with this in mind.

Reply 3: In writing this manuscript and extensively reviewing the literature, we found very few studies analyzing gender in thoracic malignancies other than non-small cell lung carcinoma. This is not to say that gender does not play a role, but simply that it has not yet been studied. We have revised the paper to emphasize lung cancer as the primary focus of the review, and included a short paragraph about other thoracic malignancies to acknowledge the existing data (page 12-13 , “*Other Thoracic Malignancies*” section).

Comment 4: Also, what type of lung cancer are you referring to? Small cell, Non-small cell? Primary lung cancer? Metastatic lung cancer? Please define more precisely. (Obviously this reviewing team knows the answer)

Reply 4: We appreciate the comment and have changed the manuscript to clearly and consistently establish non-small lung cancer as the primary focus as this is where the majority of the data exists.

Comment 5: Also, we don’t think that Figure 1 adds essential information here. You could use the same information in the text (where you could explore the concepts you wrote in Figure 1, making your introduction more exciting and preparing the reader for what is coming next in your paper).

Reply 5: We agree with the reviewer that Figure 1 does not add any additional information. We have deleted the figure and instead revised the table as suggested by a previous reviewer in order to have some visual aid accompanying the narrative.

Comment 6: **Materials and Methods:** When you did your Pubmed search, you added so many terms. Then we can see in your paper that you focused your research mostly on lung cancer, a

small amount on esophageal cancer, and almost nothing about other intrathoracic malignancies. Is there any gender implication for mediastinal tumors? Again, we are asking this because your title is broad.

Reply 6: Indeed, the focus of our paper changed as we reviewed the literature. While we initially planned to review the role of gender broadly in all thoracic malignancies, it quickly became apparent that the literature is lacking for many of these types of cancers and that the most robust data was in lung cancer. We have revised the scope of the paper and the title to more accurately reflect this.

Comment 7: In addition to this, and since you did your Pubmed research with so many terms, we wonder why you added “chemotherapy” and did not add “radiotherapy” as well. Was there a reason for that? Please refine your search and the data to include this. It would be important to capture any papers looking at stereotactic radiation by including this search parameter.

Reply 7: Thank you for noticing this, we did include radiation and radiotherapy as part of our search but we were remiss in not including the term in our methodology. This has now been revised. While stereotactic body radiation did not show up in our initial searches, we have now included a short paragraph specifically on SBRT and the role of gender (page 12 paragraph 2).

Comment 8: Why was the search performed on manuscripts published after the year 2000. Please comment on this rationale.

Reply 8: Anecdotally, most of the data on gender and lung cancer has surfaced after the year 2000. Since we focused on outcomes and also the increased rates of lung cancer in female patients, we wanted to include data that was most up to date for a contemporary review. We believe that studies on outcomes published prior to the year 2000 would reflect treatment options and other biases present in the 1980’s and that including data prior to those years would not accurately represent the current state of diagnosis and treatment of lung cancer.

Comment 9: Cancer risk: Smoking and Lung Cancer: We honestly do not think that Table 1 is bringing enough information, and we would suggest you add that information in your text instead. There, you would be able to explore the items that you wrote in Table 1, making things more exciting and easy to understand.

Reply 9: We agree with both reviewers who pointed out problems with the Figure and Table. We were hopeful that a visual aid would help summarize the information, but agree that both the figure and table do not accurately portray the results of a narrative. We have elected to remove the visual aids following both reviewers’ recommendations, but we would be open to any other suggestions.

Comment 10: We also do not understand the message you want to send at the end of this section, on page 4, “But tobacco does not explain everything. Women’s survival is higher than men’s, despite being more susceptible to the effects of tobacco”. Please clarify.

Reply 10: The sentence has been re-organized to elucidate the point that there are other gender differences apart from the use and susceptibility to tobacco that contribute to differential outcomes between men and women.

Comment 11: Do you think that can be differences between the stages at which NSCLC

diagnosis happens in Men and Women? Please comment Non-smoking risk factors for thoracic malignancies

Reply 11: Indeed, there are differences that cannot be fully explained by smoking patterns. Women tend to be diagnosed at an earlier stage compared to men, have more adenocarcinoma and higher prevalence of EGFR mutations. Page 6 paragraph 2 as well as page 10 paragraph 2 describe these differences and provide references for this difference.

Comment 12: Overall well written. We still think that the information that you display in Table 1 (and you refer to Table 1 here in this section again) would fit better if you, instead, write about the items in the text, as you did for hormonal, occupational exposures, radon, etc.

Reply 12: As discussed above, based on the comments from multiple reviewers, we have removed the table.

Reviewer D:

Comment 1: Screening and Diagnosis: Lung Cancer: We think this is the best part of your review. Well-written and covering the topic of screening extensively.

Reply 1: We appreciate the comment.

Comment 2: Esophageal Cancer: The only issue for us is that you became “a victim of your title.” Since you want to discuss Thoracic Malignancies, you reviewed a lot about Lung Cancer and briefly about esophageal. You should mention for the reader if there are other screening efforts for other malignancies (if they exist). Or again, as a friendly suggestion, you could narrow your review paper about Lung Cancer.

Reply 2: Indeed, as discussed above, we have narrowed the focus and only briefly mentioned other thoracic malignancies, without making them the focus of the paper.

Comment 3: Medical Therapy for Thoracic Malignancies: Lung Cancer: Overall liked this area, and we have only one issue to discuss. When you wrote: “the treatment modalities are anecdotally different between genders. For example, men are more likely to receive radiotherapy as the first line, while women more likely to undergo surgery, although this difference alone does not explain the higher survival in women” – Don’t you think that you may be comparing patients submitted to treatment for lung cancers potentially at different stages? Your reference is a paper published in 2005 – Reference 57 – and our question is: can you consider this information still updated to current practices?

Reply 3: You are indeed correct to point out that the data presented in reference 57 and its implications are likely outdated. We have clarified this in the body of the text (page 11 paragraph 1) and emphasized the questionable validity of the statement given the years of data collection. This provides another answer to comment #7 Reviewer C regarding the choice of year of publication.

Comment 4: Esophageal Cancer: You briefly review it, and we wonder if you have any data about any additional “thoracic malignancies.”

Reply 4: As discussed, we have narrowed the focus of our review to lung cancer specifically.

Comment 5: Surgical Care: Lung Cancer: When you wrote that “women are more likely to

undergo a more limited surgical resection compared to men,” your reference number 68 is about Stage I Lung Cancer. Does this matter? This is somewhat of a rhetorical comment on our part. Limited resection may have a role as we all know. This needs to be expanded on to drive the point you are trying to make.

Reply 5: That is an excellent point and we have revised the sentence accordingly in page 13 paragraph 2 to say: *“There is certainly a role for limited sublobar resection for stage I NSCLC and for patients with significant comorbidities or limited pulmonary function which make them medically unfit for lobectomy. However, the fact that there is a difference in the type of surgical resection as a function of gender is alarming. Furthermore, women with advanced disease (Stage III/IV) have been shown to have a lower a likelihood to receive referrals to cancer care (including thoracic Women had significantly lower rates of postoperative cardiovascular and pulmonary complications and overall post-operative survival in women, surgeons) compared to their male counterparts.(72).”*

Comment 6: You then go on to mention that “these findings may be in part because women have been shown to have a lower likelihood to receive referrals to cancer care.” Then you referred to a paper that focused on patients with Stages III and IV. Although the rationale is on point, we don’t think that the comparison that you are trying to do here is reasonable.

Reply 6: Indeed, that seems confusing and have therefore clarified this on page 13-14 to say: *“Furthermore, women with advanced disease (Stage III/IV) have been shown to have a lower a likelihood to receive referrals to cancer care (including thoracic Women had significantly lower rates of postoperative cardiovascular and pulmonary complications and overall post-operative survival in women, surgeons) compared to their male counterparts.(72)”*

Comment 7: In follow-up to that, when you discuss perioperative and postoperative outcomes between men and women, you mentioned that “women had significantly lower rates of postoperative cardiovascular and pulmonary complications and overall postoperative survival.” But in the paper used as reference (69), there was a difference in pathologic stage distribution between genders ($p < 0.001$), with a higher proportion of women having pathologic stage I disease, relative to higher stages, as compared to men. Please expand on what you are getting at here or clarify for the reader who does not pick up on this.

Reply 7: Thank you for highlighting this. Given the dearth of literature regarding gender differences perioperative and postoperative outcomes after lung cancer resection, we have chosen to keep one of the few papers that does attempt to investigate such differences. Many other references refer to gender differences only anecdotally rather than as a focus of investigation.

We revised our discussion of this manuscript to highlight the fact that men did have a higher pathological stage. Please see revised page 14 paragraph 3 to say: *“An STS General Thoracic Database study demonstrated that women had lower in-hospital and 30-day mortality (O.R. 0.56, 95% CI 0.44-0.71; $p < 0.001$). (71) Women had significantly lower rates of postoperative cardiovascular and pulmonary complications and overall post-operative survival in women, however it is important to note that men did have a higher pathological stage.(71)”*

Comment 8: After this, you mention pain and narcotic use after surgery, and you said that no difference was seen between gender, using a reference (73), which is about minimally invasive

surgery. Right after, you mentioned that “women had significantly greater pain,” and you used a reference (74) where major thoracotomy was the approach used. Can you compare both? Generally, you should be forthright with these things and not try to “pull the wool over” the readers’ eyes.

Reply 8: We certainly did not intend to create the impression of a direct comparison. We have revised page 14 paragraph 4 to read: *“In a study investigating 1164 patients (601 of which were female), no difference was seen in perioperative pain levels between men and women who underwent minimally invasive surgery(75). A smaller study investigating 157 patients who underwent resection via a major thoracotomy (62 of which were female) reported that women had significantly greater pain in the perioperative setting as well as following discharge.(76)”*

Comment 9: And in this section, you narrow your “Surgical Care” for Lung Cancer only, excluding other “Thoracic Malignancies.” Please add in the data for other malignancies.

Reply 9: We have revised the focus of the paper as mentioned to primarily reflect lung cancer.

Comment 10: Clinical Trials and Health Research: Overall well written, maybe too concise. Certainly, room to expand.

Reply 10: We agree that this section is only a brief overview, however this is an extensive topic and we are already constrained by the word limit.

Comment 11: And also, in your second paragraph, we would change “especially those who are pregnant” for ‘especially those who are in childbearing age or pregnant.’

Reply 11: This has been revised.