Author’s response to reviews

Title: Effect of metastatic site on survival in patients with neuroendocrine neoplasms (NENs). An analysis of SEER data from 2010 -2014

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Author’s response to reviews:

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To the editor and reviewers,

Happy holidays, thank you very much for considering our paper and many thanks to the reviewers for the thoughtful comments. We have amended the paper according to the suggestions. A point by point response follows.

Best regards,

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Reviewer 1 (Min Fan):

In this study, the authors used the SEER database and identified NENs patients diagnosed between 2010-2014 and assessed the impact of tumor origin and the location of metastasis in survival. I have several concerns.

1. In this study, for Lung NEN patients, the histological grade classification is not suitable. According to the 2015 WHO classification, Lung NEN patients should be classified into typical carcinoid, atypical carcinoid and large cell NEC (LNEC).

Author response: This is actually a correct observation. Staging/grading is always a huge discussion in neuroendocrine neoplasms and lung neuroendocrine neoplasms are indeed commonly classified as atypical and typical carcinoids, large cell neuroendocrine neoplasms and small cell lung cancer.

In this study excluded small cell lung cancer, which otherwise is a high-grade neuroendocrine neoplasm, because of its very unique and well-studied behavior and acknowledge that this might affect the results of our study (line 167). SEER will code small cell lung cancer and large cell neuroendocrine neoplasms, as well as typical and atypical histology (for all histology types, not just lung). We have included that distinction in our descriptives and in our analysis (univariate and multivariate). For example, in Table 1, you can see the histology classification.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>496</td>
<td>24.74</td>
</tr>
<tr>
<td>Atypical/ high grade</td>
<td>1487</td>
<td>74.16</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>22</td>
<td>1.1</td>
</tr>
</tbody>
</table>

For survival purposes, SEER analyses have relied on grade (well/poorly and low/high) classification to produce metrics. An example is the seminal Yao paper and the most recent Dasari paper in JAMA Oncology (attaching screenshot/ also a reference). The agreement is that G2 correlates with moderately differentiated or atypical, although that is not always the case, while G3 is poorly differentiated (or large cell/small cell).

We have amended the methods (line 102) and discussion to acknowledge those shortcomings (Line 167). We have also included typical/atypical histology and grade as separate important factors in our score, as per multivariate analysis results (see below Table 3). The independent importance of grade, typical/atypical histology and site of metastasis is preserved. Thus, one can surmise that atypical lung neuroendocrines will have worse survivals than typical ones, and that regardless of that, respective metastatic sites will affect the survival.
We furthermore believe that ultimately lung NENs will be graded similarly to GI NENs because higher proliferation rates are associated with progressively more virulent behavior. Some literature supporting that is Pelosi et al, Thorac Oncol. 2014 (PMID 24518085), Rekhtman et al in Mod Pathol. 2019 (PMID 30923345). That last paper moreover acknowledges that “WHO classification was developed for resected primary carcinoids, whereas its applicability to stage IV setting is not well established”. We added those references and discussion as of Line 170.

2. WHO Classification 2017 of neuroendocrine organ has published. And for pancreatic NEN, NET (according WHO 2017) has to be distinguished in three subcategories according to Ki-67 labelling index : NET G1 <3%; NET G2 3-20% and NET G3 >20%. Never authors distinguish NET according to these strongly validated WHO rules. Actually, Pan-NEN should be divided into well-differentiated Pan-NET (G1, G2 and G3) and poorly differentiated. I suggested that Pancreatic NEN be excluded from this study, because the author might not be able to reclassified them according to the 2017 WHO criteria by using the SEER database. What is the authors' concerns.

Author response: We definitely share this concern; Classification of tumors will change over time but SEER submissions will not unfortunately be amended retrospectively. For example, as of most recent WHO classification, all GI histologies will follow the pancreatic paradigm (i.e. including a well differentiated high grade category. NET-G3), as you mentioned. It is a similar problem with analyses that include the TNM status (which doesn’t commonly change over time) and staging (which can).

The SEER database will record tumor differentiation status and grade as per criteria at the time of submission. SEER includes typical and atypical histology as well, so these variables have been used in our analysis and are statistically significant. One can assume that the new well differentiated Grade 3 category would fall under “typical + G3” or “atypical + G2”, although that is not absolute. In our multivariable analysis we tried to account for all of these variables. We discuss some of the shortcomings in line 174. As mentioned above, large retrospective studies using SEER have used grade for their cumulative results, again with the same reservations.

At the end of the day, the main point of the paper is to show that independent of the above subcategorizations, metastatic sites play an independent role in prognosis and we have been able to show that for any differentiation and grade combination. So we would prefer to keep the pancreatic data in our results, because we believe they are important.

3. M stage analysis using data base is very difficult. As written in Collaborative Stage Transition Newsletter (January 19th, 2016), many pM0 may include case with cM1, because pathologists did not assess metastatic site without specimens, and in consistent coding practice and data loss is found. Therefore, many bias can be exist in this study. Moreover, data in this study included many Nx cases.

Author response: We agree that large retrospective studies based on databases might miss occult metastatic disease. As the author noted, and as stated in the Collaborative Stage Transition Newsletter “Upon abstraction, the registrar has no way of recording the appropriate M category for the pathologic stage if it is cM1. This discrepancy between registry software data items and AJCC staging classification rules causes a dilemma for registrars when abstracting the T, N, and M data items and results in inconsistent coding practices and data loss.”
In this study we focused on SEER patients with established metastatic disease (this was the new coding in SEER we were able to take advantage of). We do not know if that M1 status was pathology or image determined, but it was single site and unequivocal. We also have coded about 13% missed N cases but we feel that this is less relevant, since the presence of metastasis trumps the unknown LN status survival-wise. We have made the relevant clarifications in the discussion Line 210.

Reviewer 2 (Sebastian Krug): Interesting study by Trikalinos and co-worker. Of course, there are already known data and in principle the results are not surprising, as other studies have already drawn the same conclusions. Here, however, the difference in data quality and form of data acquisition in a register is again evident compared to monocentric or retrospective multicentric national studies.

Compared to the currently published studies, the rate of brain metastases is very high at 6% and the rate of bone metastases rather low at 7%. This should be better discussed more in detail in comparison to the given literature.

Author response: This is a very nice observation. The rate of skeletal metastases is close to 10% for neuroendocrine tumors as a whole), and even though in the past it was thought that certain only histologies might show a preference for skeletal metastases, this has been challenged. Our original database included 34704 nondescript NEN patients and metastatic sites included brain (2.99%), bone (4.63%), liver (14.82%) and lung (4.10%). Details are available upon request. In our attempt to use as clean a specimen as possible, we only included patients with known single site metastasis. This has led to an enriched database and some unusual percentages. We have amended the body of the manuscript to account for that (Line 187).

SCLC was excluded according to the methodology. Ultimately, the spread of metastasis is already dependent on primary tumor localization. In this respect, a distinction between Primarius lung and non-lung would be interesting.

Author response: Agree that the spread of metastasis is heavily dependent on the origin of the tumor. In our analysis, median survivals for single site brain metastasis was recorded in lung and “other” section, while pancreas showed mainly liver and bone metastases. That being said, median survival was same for brain metastasis in “lung” and “other” and the multivariate analysis showed an independent effect of metastatic site (with reference to tumor origin). We have clarified this better in the paper in line 184 but agree that, ultimately, the data is insufficient.

B. Median survivals by tumor and metastatic site in years

<table>
<thead>
<tr>
<th>Tumor of origin</th>
<th>Median</th>
<th>M-lung</th>
<th>M-liver</th>
<th>M-bone</th>
<th>M-brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>0.83</td>
<td>2.92</td>
<td>0.67</td>
<td>0.75</td>
<td>0.58</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3.5</td>
<td>N/A</td>
<td>3.5</td>
<td>1.33</td>
<td>N/A</td>
</tr>
<tr>
<td>Small bowel</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Other</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>0.58</td>
</tr>
</tbody>
</table>